TIME TO SURGICAL DEBRIDEMENT IN OPEN LONG BONE FRACTURES OF THE LOWER LIMB AND ITS EFFECT ON UNION AND INFECTIONS – A PROSPECTIVE COHORT STUDY

Dissertation submitted in partial fulfillment of the requirement of The Tamil Nadu Dr. M.G.R Medical University for the M.S. Orthopaedics Examination to be held in May 2018

CERTIFICATE

This is to certify that the dissertation titled, "Time to surgical debridement in open long bone fractures of the lower limb and its effect on union and infections – A prospective cohort study'' is a bonafide work of Dr. Christina Marie Joseph in partial fulfillment of the requirements for the MS Orthopaedic examination of The Tamil Nadu Dr. M.G.R University Examination to be held in May 2018.

GUIDE

Dr. Thilak Samuel Jepegnanam,

D.Ortho & M.S Ortho, MMedSc(Otago)

Professor and Head of Unit III

Department of Orthopaedics

Christian Medical College, Vellore

SELF

Dr. Christina Marie Joseph

Post Graduate Registrar

Department of Orthopaedics

Christian Medical College, Vellore

PRINCIPAL

Dr. Anna B Pullimood

Christian Medical College, Vellore

HEAD OF THE DEPARTMENT

Dr. Vijay TK Titus,

D.Orth, M.S Ortho, DNB (Ortho)

Department of Orthopaedics

Christian Medical College, Vellore

DECLARATION

This is to declare that the dissertation titled, "Time to surgical debridement in open long bone fractures of the lower limb and its effect on union and infections – A prospective cohort study'' in partial fulfilment of the requirements for the MS Orthopaedic examination of The Tamil Nadu Dr. M.G.R University Examination to be held in May 2018 comprises of my original research work and information taken from secondary sources has been given due acknowledgement and citation.

Dr. Christina Marie Joseph,

Post Graduate Registrar

Department of Orthopaedics

Christian Medical College, Vellore

ACKNOWLEDGEMENTS

At the very outset, I would like to acknowledge my guide, Dr Thilak Samuel Jepegnanam for his passion in the field of trauma and commendable effort in initiating this dissertation, making it possible to work on a topic that was of great interest to me. I express my deepest gratitude for his untiring, invaluable assistance, encouragement and guidance at every step.

I would like to thank Dr V.T.K Titus, Professor and Head of the Department of Orthopaedics, CMC Vellore for his constant help and support. I take this opportunity to thank Dr Boopalan Ramasamy for his brilliant and innovative ideas, Dr Vinoo Mathew Cherian for his undue patience, benevolence and perseverance till the completion of this dissertation and Dr Manasseh Nithyananth for his profound suggestions and advice.

Dr Thambu David Sudarsanam, Professor and Head of the Department of Medicine Unit-2 played a pivotal role in organizing the study methodology and in the statistical analysis despite his busy schedule. I wish to thank Dr Prasanna S Premkumar from the Department of Biostatistics for analysing the data. I thank the Institutional Review Board and Fluid Research Committee of CMC Vellore for granting me permission to conduct this study and for the financial assistance provided.

I extend my gratitude to my family, especially my parents for their unwavering encouragement. My heartfelt thanks to my elder sister, Philomeena, for being my guiding light throughout.

I am forever grateful to the Lord Almighty for all the above mentioned people and the countless blessings that he has showered on me. Finally, I thank all the patients who participated in this study.

URKUND

Document	TIME TO SURGICAL DEBRIDEMENT IN OPEN LOWER LIMB FRACTURES.docx (D31385669)
Submitted	2017-10-17 03:39 (+05:0-30)
Submitted by	Christina Marie Joseph (christina_j3@yahoo.com)
Receiver	christina_j3.mgrmu@analysis.urkund.com
Message	Show full message
	0% of this approx. 32 pages long document consists of text present in 0 sources.

INTRODUCTION

Surgical debridement in open fracture is an orthopaedic emergency and requires timely management. Exposure of the bone with lack of soft tissue cover and alteration in blood supply, decreases oxygenation providing an anaerobic environment favourable for bacterial growth (1). Further, time delay in surgery could also increase local spread of the contamination, making adequate debridement a challenge for the treating surgeon. In 1898, Friedrich et al demonstrated that surgical debridement of wounds beyond 6 hours from injury were associated with an increased risk of mortality and death (2–4). Subsequently, In 1973, Robson et al defined "open fracture infection threshold" and found it to reach within a mean of 5.17 hours following the injury (5,6). Though traditional guidelines suggest urgent surgical debridement within 6 hours, recent studies have reported no difference in occurrence of complications with regard to early versus late debridement (7–10). Further, the better availability of anaesthetists and surgeon's in the trauma team during the day time reflects an increasing trend to postpone the surgeries till the next day morning. However all these studies were conducted in the West where contamination rates in open fractures are expected to be low. This is probably due to the cold climate with decreased chances of enhanced microbial colonization in open wounds. We felt that late surgical debridement may not be appropriate in a hot tropical Third World country like India where patients often present late with grossly contaminated wounds. With the increasing number of road traffic accidents and large number of referrals, we expect that a time delay in debridement of open fractures would have detrimental consequences. We thus conducted a prospective study on open long

CONTENTS

INTRODUCTION

Surgical debridement in open fracture is an orthopaedic emergency and requires timely management. Exposure of the bone with lack of soft tissue cover and alteration in blood supply, decreases oxygenation providing an anaerobic environment favourable for bacterial growth (1). Further, time delay in surgery could also increase local spread of the contamination, making adequate debridement a challenge for the treating surgeon.

In 1898, Friedrich et al demonstrated that surgical debridement of wounds beyond 6 hours from injury were associated with an increased risk of mortality and death (2–4). Subsequently, In 1973, Robson et al defined "open fracture infection threshold" and found it to reach within a mean of 5.17 hours following the injury(5,6). Though traditional guidelines suggest urgent surgical debridement within 6 hours, recent studies have reported no difference in occurrence of complications with regard to early versus late debridement (7–10). Further, the better availability of anaesthetists and surgeons in the trauma team during the day time reflects an increasing trend to postpone the surgeries till the next day morning.

However all these studies were conducted in the West where contamination rates in open fractures are expected to be low. This is probably due to the cold climate with decreased chances of enhanced microbial colonization in open wounds. We felt that late surgical debridement may not be appropriate in a hot tropical Third World country like India where patients often present late with grossly contaminated wounds. With the increasing number of road traffic accidents and large number of referrals, we expect that a time delay in debridement of open fractures would have detrimental consequences.

We thus conducted a prospective study on open long bone fractures of the lower limb to evaluate the association between a time to initial surgical debridement and development of non-unions and infections.

AIM

To evaluate the association between time to initial surgical debridement and development of non-unions and infections in open long bone fractures of the lower limb.

OBJECTIVES

1) To evaluate the association between time to surgical debridement in patients with open lower limb fractures and the incidence of non-unions (assessed at 9 months) and to compare the non-union rates in 2 groups of patients (early and late) based on the time to debridement (less than or more than 12 hours from injury).

2) To analyse the effect of time delay in surgical debridement on the development of infections and compare the infection rates in the 2 patient groups.

3) To compare the average number of secondary surgical procedures in both patient groups.

4) To analyse the number of re-admissions, duration of hospital stay, inpatient bills and other complications in both patient groups

5) To assess the functional outcome of patients in both groups at 9 months follow-up using health based scoring questionnaires. (SF-36 and SMFA scores) (11, 12).

HYPOTHESIS

Recent literature from the West supports late debridement in open fractures with acceptable outcomes (7–9). We felt that this may lack validity in our setting. In contrast to developed countries where open fractures are principally low energy injuries resulting from falls or crush injuries, road traffic accidents have been found to be the leading cause of open lower limb fractures with incidence rates varying between 70-90% in developing countries (13–17). Motor vehicle accidents have been associated with high rates of mortality and deaths (17–19). In a densely populated hot tropical country like India, large numbers of referral patients often present late with gross contamination of wounds. We anticipate a higher risk of bacterial colonization of wounds and infectious complications with a delay in fracture healing if not addressed early.

We thus hypothesized that in our setting a delay in time to surgical debridement would significantly affect fracture union, infection rates and patient quality of life.

LITERATURE REVIEW

Open fractures: -Evolution of treatment

The Edwin Smith papyrus, the oldest trauma treatise from ancient Egypt was translated in 1920 and provides the earliest documented evidence on the principles and practice of orthopaedics surgery and management of fractures dating back to 1,300 BC (20–22).It also contains data on open wounds and soft tissue coverage. Hippocrates (460–477 BC), a Greek physician and surgeon was the first to describe management of wounds (2,23,24). Open wounds communicating with fractures and extensive soft tissue injury were considered risky and difficult to treat. He believed that these injuries associated with vascular and soft tissue damage were complicated to manage and were less likely to have a favourable outcome. Aggressive treatment of these wounds would cause more harm than benefit and were best left alone. He also advocated that wounds should be kept dry and periodically cleansed with clean water, honey or wine. Suppuration of wounds meant healing with extrusion of undesired and spoiled blood. Claudius Galen (130–200 AD), later used the Latin term "pus bone et laudabile" which translated into "laudable pus" which essentially meant that suppuration in wounds was a good sign and hastened wound healing (2,23,25). He popularized the practice of Hippocrates and proved that suppurating wounds healed faster. Dominican friars Theodoric (1205–1296), later asserted that formation of pus in wounds were not a necessity in healing wounds.

Historically, much of the knowledge of treatment of open fractures evolved from management of injuries sustained in military warfare(23, 24). Gunpowder was introduced in Europe during the 14th century and Heinrich Prolspeadlt reported the first gunshot wound in 1460.(25). These injuries were particularly challenging to manage given the high velocity of the impact potentially damaging to soft tissue. Extensive muscle injury with compromised blood supply and tissue oxygenation provided a favourable environment for bacterial growth. It was observed that several patients with open fractures expired early because of uncontrolled haemorrhage and those who survived invariably died from sepsis within a month (27).With the lack of knowledge of bacteria and wound colonization in that era, it was believed that wound infections were a consequence of the poisonous material in the gunpowder. This led to the practice of pouring boiling oil on wounds to destroy the poison.

Ambroise Paré (1510–1590) was a French Army surgeon and believed in concept of treating open wounds with boiling oil to purify them. However due to the shortage in oil supplies he designed his own pastes containing egg yolks, rose and turpentine oil and reported the success of this in many wounds. Later treatment of wounds with wine and pig lard was also used and was popularized till the 17th century (25,28).

On 22 April 1676, Admiral De Ruyter, a famous Dutch sub commander in the merchant navy sustained a severe open fracture of the right lower leg during a naval battle near Mount Etna (25). As per the existing practice of wound care, his wounds were treated with brandy and he was advised rest for limb immobilization. However he developed fatal gangrene of his limb over a span of few days. This led to the thinking that conservative treatment of wounds with local dressings was not sufficient and these needed to be surgically addressed these in order to remove foreign bodies and drain undesirable pus. This was probably how the concept of wound debridement was born.

Later, both John Jones (1729–1791) and Desault (1738–1795) who were military surgeons, advocated the need for surgical treatment of wounds in the 18th century (29). They devoted much of their time to teaching young military surgeons and educating them on the importance of adequate wound cleansing and surgical debridement. John Jones also asserted the need for splinting of fractured limbs along with surgical care of wounds to stabilize soft tissue and bone and minimize bleeding.

Louis Pasteur (1822–1895) introduced local wound antiseptics and use of carbolic acid for wounds. The success of using antiseptics made the practice of surgical debridement less necessary in the 18th century. Only wounds with extensive soft tissue damage were surgically treated. The use of antiseptics was widespread during the Franco-Prussian War (1870-1871).(23, 28, 29).

Subsequently, Alexis Carrel (1873–1944), a French surgeon saw the need for decontamination of wounds when he increasingly witnessed several infected open fractures. He worked along with an English chemist Henry Drysdale Dakin (1880–1952). They were instrumental in introducing the Carrel-Dakin method of wound management (25,32). It was composed of a weak neutralized solution of sodium hypochlorite and boric acid (which was known as Dakin's solution) Use of antiseptics in wound management was a forerunner to invention of antibiotics later.

However, it was observed that the practice of directly instilling antibiotics in wounds also had minor complications like local skin irritation and its use in highly contaminated wounds without emphasis on surgical management was questionable. Around the same time, a Russian army surgeon Carl Reyher advocated the importance of surgical wound care along with antiseptics and showed that the mortality rate in gunshot injuries reduced from 66% to 23% (25). Nevertheless, the success and use of antiseptics had already shifted the practice of wound management from surgical to medical till the Great War (World War I) (29)

Until World War I, it was believed that antiseptics were the mainstay of treatment and required only minimal surgical procedures and cleansing. With the culmination of World War I, new destructive machinery and equipment were manufactured (28, 29). Thus with the advent of modern technology, the fire-arms and artillery used in World War 1 were far more advanced. High explosive shells were used weighing nearly a ton. Further the fragments from the shrapnel were of varying size and far more damaging to the soft tissue (29). The incidence of injuries from machine gun small arms peaked to 46% as opposed to 14% in previous battles. To add to the wound problems, most of the trenches were dug in the soil and some wounded soldiers lay there for days unattended. This led to increased number of deaths from haemorrhage and sepsis (29).

Antoine Depage (1862–1925) revived the principles of wound debridement and emphasized that it was not a simple procedure but included both incision of wounds and extensive removal of dead necrotic tissue (29). He also advocated delayed primary closure of contaminated wounds and stated that wounds should be closed only after infection control (30).

The concept of biological wound debridement was put forward by William S. Baer (1872–1931). This was based on his experienced gained from 2 soldiers with open lower limb fractures in 1917 during World War I (23, 31). One of the soldiers sustained a compound open femur fracture and multiple wounds over his abdomen and scrotum with large soft tissue defects (23). Both victims were left unattended to for several days on the battlefield without even food or water for survival. After adequate medical attention was given they were brought to the hospital, Baer observed that on removal of their clothes, the open wounds were filled with thousands of maggots and there was no direct exposure of the bone. Instead, pink healthy tissue that later came to be known as granulation tissue enveloped and completely covered the bone. Baer later used sterile maggots in the treatment of patients with infected wounds and chronic osteomyelitis.

He also demonstrated that a time period within 12 hours from injury for wound debridement was essential for complete removal of dead necrotic tissue, beyond which the wound could no longer be considered aseptic and primary closure wound not be possible. He showed that this rule of early wound debridement was successful in 80-95% of the wounds and was able to achieve primary wound closure in these patients with minimal complications. However when transportation facilities were scarce and wounds were debrided late, he suggested delayed secondary closure.

Much later surgeons were able to distinguish the type of discharge from wounds and pus was no longer considered to be necessary for wound healing (23, 30). The initially known “laudable pus” was limited only to creamy or serous discharge from wounds which was not foul smelling whereas the thick yellow, blood-stained discharge was deemed as malignant and associated with sepsis and death (23).

Mobile Army Surgical Hospitals (MASH) were widespread during the Korean War (1950–1953) Thus patients were immediately transported from the battlefield and wounds were managed within 2-4 hours from the injury. The standard practice of wound care for victims of the Korean War included antibiotic prophylaxis using penicillin and streptomycin, adequate wound debridement and delayed closure of wounds (25, 32).

Transportation facilities were refined even further during the Vietnam War (1959–1975) where helicopters were used for rapid transport of patients. Thus surgical wound care could be administered within 1 to 2 hours (32). External fixators were used for wounds with large soft tissue defects.

During the United States ‘invasion in Panama (1989–1990) there were 9 reported infected open fractures out of 37 open fractures. There were a total of 18 type III injuries, 9 of which underwent debridement at Panama and the remaining in the United States It was reported that only 2 of the fractures treated at Panama itself got infected as opposed to 6 out of 9 treated at the United States. This emphasized the need for early wound debridement (23).

Lower extremity fractures are till date one of the most common injuries encountered in warfare. During the prolonged Iraq and Afghanistan conflict (2003-2014), 58% of all the lower limb fractures were open with tibial fractures being the most common (33).

Open fractures as a consequence of both battlefield injuries and high-energy civilian trauma are equally challenging to manage and literature states that they should be invariably considered and treated as contaminated grade 3 fractures to reduce the mortality associated with them which mainly includes infections and late amputations (33,34). The increasing complexities of wounds in high energy trauma necessitate strict practice of the principles of surgical debridement.

Amputations in war history

Historically amputations were considered the only resort and hope in open fractures to save lives. Sushrata and Hippocrates stated that distal limb amputations could be tolerated well and obviated need for use of a tourniquet to control bleeding. Later Celcus, a Roman surgeon popularized the technique of ligating major vessels during amputations to control bleeding (32,35).

John Jones (1729–1791) was the first to emphasize the importance of life over limb in his textbook published on management of surgical wounds and fractures during the American independence war. He advocated that the need to amputate limbs as part of a lifesaving procedure was primarily the decision of the operating surgeon. The emphasized on life before limb and the need for adequate debridement (25,32).

Later, both Desault and Larry described surgical techniques in wound management and conducting amputations. Primary amputations were performed with the intention of controlling haemorrhage. Larry performed most of the surgeries on the battlefield itself thus saving the lives of large numbers of wounded soldiers (36).

During World War 1, the principles of wound management using antiseptics along with surgical debridement were still evolving. Thus the rates of secondary amputations as a result of sepsis were almost as high as that of primary amputations (28%). The reported number of amputations performed during the First World War were between 3-5 lakh (35).

Robert Jones popularized immediate splinting of fractured limbs to control bleeding during World War 1. With the contributions of both Robert Jones splinting technique and surgical debridement principles of Antoine Depage, amputations due to haemorrhage and sepsis drastically reduced.

However the problem encountered during the Second World War was major vessel vascular injuries. 50% of these injuries resulted in amputations. The popliteal artery was found to be most commonly involved and results of ligation versus repair showed no difference in outcome. Limb salvage thus became difficult. However with improvement in the knowledge of anatomy, due importance was given to repair of the popliteal artery. Analysis of lower limb vascular injuries during the Korean War showed a 75-80% reduction in amputation rates as compared to that witnessed during the Second World War. (35).

Over the latter years of the 20th century, the proportion of major amputations due to infection and vascular injury has been reported to have significantly decreased from 30-40% to 10%. Thus amputations were no longer considered the only hope for survival in lower limb fractures and focus was directed towards limb salvage. This led to the introduction of the MESS score.

The Mangled Extremity Severity Score (MESS) was developed by Kaj Johansen, a vascular surgeon at Seattle along with Sanders in 1990 (37, 38). This was based on his observation of the increasing number of deaths in patients who were victims of high energy trauma involving the lower extremity where limb salvage was attempted. He retrospectively reviewed these patients to see whether any objective or demographic data at the time of presentation to the emergency department could predict the likelihood of limb salvage After a retrospective analysis of 25 patients, it was concluded that a score ≥ 7 was 100% predictive of an amputation (37,38). The validity of this scoring system has been tested by several studies(39,40). The MESS score has 4 criteria of assessment –soft tissue injury, limb ischemia, systolic blood pressure and age of the patient. (Fig.1).

Fig.1 :- Mangled Extremity Severity Score (MESS) (37)

Mangled Extremity Severity Score (MESS) → 1-14

Skeletal / soft-tissue injury
Low energy (stab; simple fracture; pistol gunshot wound): 1
Medium energy (open or multiple fractures, dislocation): 2
High energy (high speed MVA or rifle GSW): 3
Very high energy (high speed trauma + gross contamination): 4

Limb ischemia
No ischemia: 0*
Pulse reduced or absent but perfusion normal: 1*
Pulseless; paresthesias, diminished capillary refill: 2 *
Cool, paralyzed, insensate, numb: 3*

Shock
Systolic BP always > 90 mm Hg: 0
Hypotensive transiently: 1
Persistent hypotension: 2

Age (years)
< 30: 0
30-50: 1
> 50: 2

*** Score doubled for ischemia > 6 hours** from Johansen et.al. 1990

Court Brown et al tested the validity of the MESS score exclusively in a military population where open fractures were solely the consequence of very high energy trauma. They found that the presence of a vascular injury with prolonged hypotension was the principal indication for amputation (41). They concluded that in the absence of shock or an ischemic limb, limb salvage must be attempted regardless of the MESS score.(35) .

During the Gulf War (2003), the rates of traumatic and primary/secondary amputation were each recorded as 14% (32). In a meta-analysis study conducted from 1993 to 2013, Covey et al reported that late lower extremity amputation after limb salvage varied from 3.9% to 40% in civilian patients and from 5.2% to 15.2% in military patients(34). Factors influencing a patient's decision to undergo late amputation included a combination of complex pain symptoms with neurologic dysfunction, infection, a desire for improved limb functionality, and unwillingness to endure an often complicated and lengthy course of treatment.

With the advent of modern technology and knowledge of surgical principles treatment strategies for the management of open fractures has steadily evolved. However the risk of amputations following definitive treatment especially high velocity trauma is inevitable. The decision for limb salvage versus primary amputation is dependent on the operating surgeon. It is still often debatable especially in high energy traumatic lower limb fractures, though most would follow Court Brown's guidelines which state that limb salvage should be attempted in the absence of shock or ischemia (42–44).

Epidemiology of open fractures

The estimated number of open fractures in the United Stated is 3-6 million annually (45,46) with open fractures accounting for more than 3% of these injuries (42,46). Cross et al in 2008 predicted that the number of open fractures in India was 4.5 million per year after adjustment of data to account for the population difference. However considering the rapid expanding population in urban areas, this data may not be an accurate estimate.

The incidence of open fractures is difficult to precisely determine as most literature includes studies conducted at Level 1 high speciality trauma centres that cater exclusively to the management of complex trauma. Population-based epidemiology studies are rare. Literature reports the overall incidence of open fractures to be 11.5-13.7 per 100000 persons per year(42,43,47,48) with finger phalanges being the most common followed by tibia shaft fractures. This was from data collected at the Edinburg trauma centre. Since it is the soul centre for trauma care catering to an entire population of around 70000 people, this data is a representative of the entire population (42).

Court Brown conducted a 15 year follow up study on 2386 open fractures presenting to the Edinburg trauma centre in Scotland and analysed both the incidence and severity of these injuries (43). This was one of the first documentations of the epidemiology of open fractures in a large adult population where both in and out-patients were analysed. They reported that majority of open fractures were low energy injuries. Road traffic accidents accounted for only 34% of lower limb fractures and remaining were due to falls, cut injuries or assaults. Open fractures involving the tibia were commonly seen in young males. 45% were Grade 3 injuries. The calculated average number of open fractures per year caused by road traffic accidents was 2500, with 810 being tibia fractures. The overall incidences of tibia fractures were $3.4/10^5$/year. They concluded that this data could be comparable to other countries. However this conclusion would be contested by studies from developing countries where the majority of open fractures occur.

Data published from Third World developing countries like India, China, Nigeria, Tanzania in Africa, have shown the majority of open fractures are caused by road traffic accidents.

X Qi et al in 2006 retrospectively reviewed 2213 traffic related trauma patients in Ningbo China and found that more than 50% had extremity fractures(13).

In a 1 year prospective cohort study on open tibia shaft fractures in Nigeria, 91.4% were due to road traffic accidents(14). In another recent study conducted at North Tanzania by Cleland et al in 2016, tibia/fibula shaft fractures were found to be one of the commonest reasons for hospital admissions in orthopaedics with 72% of these injuries being open (15). Motor vehicle accidents were the leading cause of trauma and accounted for 78%. They also reported that these injuries were most common in young males in the age group of 21-30 years.

Gopinathan et al reviewed 50 patients In a retrospective study conducted in North India, with traumatic lower limb vascular injuries and found that 64% had an associated open fracture (16). 84% of these fractures were caused by motor vehicle accidents. The amputation rate was higher in the presence of an open fracture (60%). Of the 3 deaths encountered, all were due to motor vehicle accidents with open fractures and complete vessel injury.

The high incidence of road traffic accidents in these countries reflects the deficiencies in their economic system with less stringent traffic laws permitting increasing number of vehicles on the road with minimal directed efforts to improve the road surface infrastructure and environment. In these countries, travel by road is a cheap and affordable means of transport for the general public. (17). The World Health Organization (WHO) Global Status Report on Road Safety 2015 stated that road traffic accidents were a major socioeconomic burden with the highest reported fatality in Africa. The reported death rates in Africa were 26.6 per 10000 per year in

2013 and accounted for over 85% of all deaths (17). According to the latest statistics from India, Road traffic accidents are responsible for 35.2% of all accidental deaths (18). Tamil Nadu accounted for maximum number of road traffic accidents (15.4%)compared to other states and the highest number of deaths (11.6%) resulting from motor vehicle trauma (18).

Given the increasing number of motor vehicle accidents in developing countries, there is a need for implementation of road safety rules to decrease the number of deaths mortality associated with open fractures.

Classification systems in open fractures

Till the early half of the 20th century, fractures were broadly categorized into closed or open. Ellis (1958) and Nicoll (1964) highlighted the importance of both soft tissue and bone in the classification of open fractures. Ellis graded the fractures as minor moderate or severe (whereas Nicoll divided them into 2 groups ("nil or slight" and "moderate or severe") (44). However the drawback was that their classification system was based purely on subjective criteria.

In 1965, Cauchoix was the first to grade fractures according to the severity of the wound and graded wounds into 3 types. Type 1 injuries were puncture wounds with minimal soft tissue damage, Type 2 injuries were those in which soft tissue damage was more and posed a risk for necrosis. Type 3 injuries included those with extensive loss of skin and subcutaneous tissue. This was followed 2 similar systems of classifications from Allgower and Anderson in 1971. These wounds however did not distinguish between soft tissue injuries with and without internal degloving. This factor was essentially important in high energy injuries where the damage caused by internal degloving is far more than that of the external skin wound.

Gustilo and Anderson sought to develop a classification system that could predict the outcome of wounds in open fractures and guidelines for management of these injuries. At this time, use of antibiotics, surgical debridement and delayed closure of contaminated wounds were well emphasized on and these principles were slowly gaining recognition in the management of open fractures. However, the way these injuries responded to treatment was variable, depending on the soft tissue involvement, velocity of the impact and contamination. There was a need for development of standardized management protocols for different types of wounds (1, 47).

Gustilo and Anderson evaluated a retrospective cohort of 673 open long bone fractures from 1955 to 1968 at Hennepin County Medical Center, Minneapolis, Minnesota (49). The antibiotics used in wound prophylaxis included penicillin, chloramphenicol, oxacillin and kanamycin. Primary wound closure was attempted whenever possible and the decision for internal fixation depended solely on the treating surgeon. The infection rates from 1955 to 1960 and 1961 to 1968 were 12% and 5% respectively.

Their study analysis did not halt here and they went on to prospectively analyse 352 patients from 1969 to 1973 (49). During this time period they graded the severity of open fracture injuries into 3 grades. Type 1 injuries included clean wounds less than

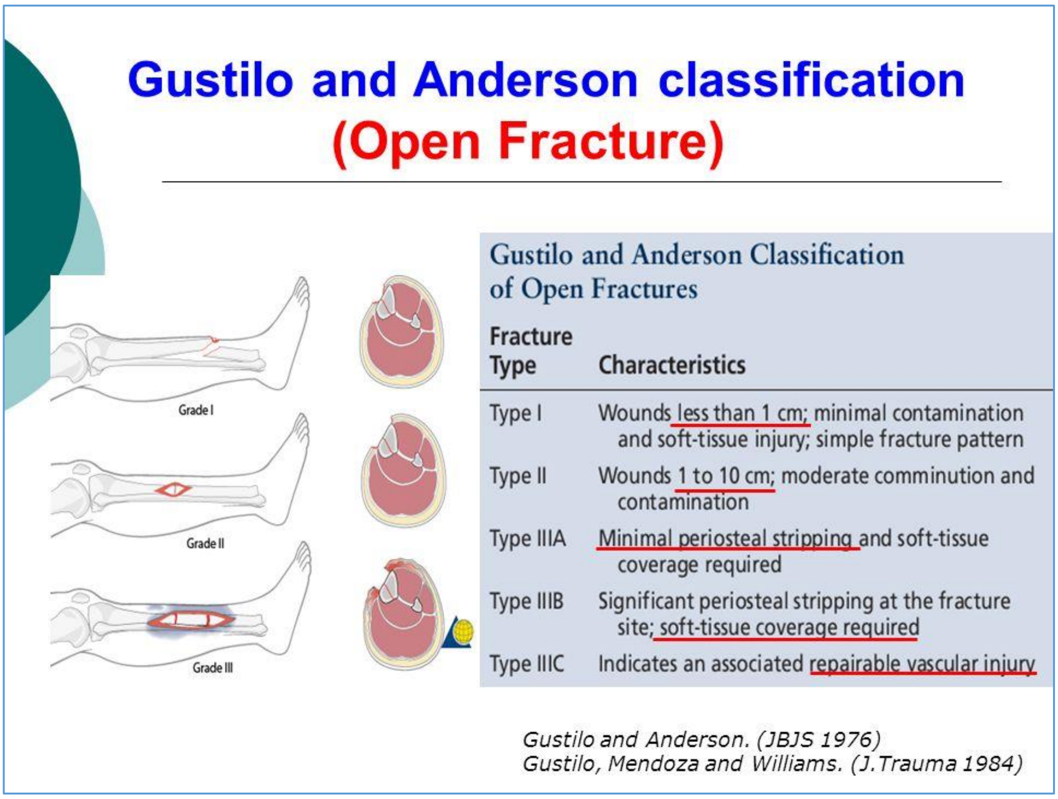
1 cm in size. Type 2 wounds had wounds more than 1 cm long. However the extent of soft tissue involvement was not severe. These included injuries without much degloving, soft tissue flaps or severe avulsions. Type 3 injuries, were the highest grade and included open fractures with segmental involvement and severe extensive soft tissue damage. This grade of injuries also included traumatic amputations, gunshot injuries and soil contaminated farmyard injuries.

All patients in the prospective study uniformly received antibiotic prophylaxis with oxacillin and ampicillin was continued for 3 days following surgery. Initial cultures were taken from all wounds. Primary closure was done for Type 1 injuries and secondary closure for Type 2 and 3 injuries. Primary internal fixation was only reserved for those with vascular injuries.

Using these guideline protocols for the management of open fractures, they reported an overall infection rate of only 9.9 % in grade fractures in the prospective study as opposed to 44% in the retrospective study. Primary internal fixation with primary wound closure had an increasing trend for development of osteomyelitis especially in Type 3 injuries. Further in grade 3 injuries, they advocated delayed closure, skin grafting and flaps for soft tissue cover. They concluded based on the initial wound cultures that the antibiotic of choice in open fractures were cephalosporins. Use of external fixation devices in open fractures resulted in lesser complications as opposed to internal fixation.

Subsequently, it was observed that there was an increasing incidence of Type 3 injuries which became challenging to manage. Further the infection rates in this group of patients were considerably higher than lower grade injuries. The overall infection rates in Type 3 fractures ranged from 10-50% (50). There were 75 patients with 87 type 3 fractures treated from 1976 to 1979 at the same centre in Minessota. This led to a modification of the previous classification fracture grades where Type 3 injuries were further sub classified. (Fig.2)

Fig.2:- Modified Gustilo and Anderson Classification (50)



An important component of the modified classification system was that the velocity of trauma was taken into account. Regardless of the wound size, all high-energy segmental open fractures were considered as grade 3. Grade 3A injuries included those with adequate soft tissue cover of the fracture site without extensive soft tissue damage. 3B injuries were those with periosteal stripping and severe contamination. 3C fractures composed of vascular damage requiring repair.

Later, several studies tested the validity of this classification system with reported intra-observer agreement ranging from 42-94% (51). Despite its limitations and intra-observer variability, the modified Gustilo Anderson classification continues to be one of the most used standardized classification systems for open fractures world-wide.

Herald Tscherne, in Hannover, Germany behaviour and biometrics of patients with polytrauma and soft tissue injuries (52). This led to the development of the Tschernes classification system. (Fig.3)

Fig.3:- Tschernes classification system for soft tissue

Tscherne classification for soft tissue injury

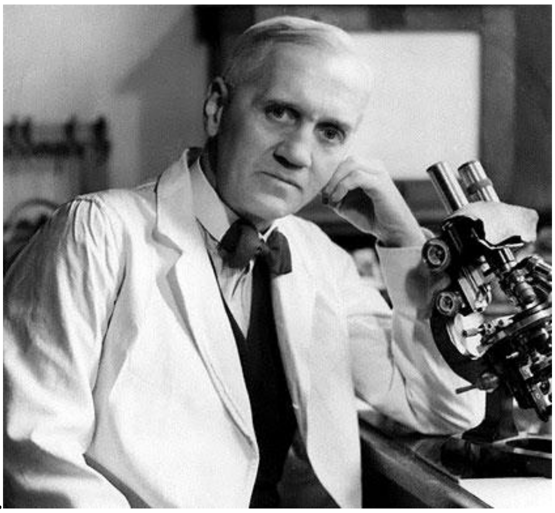
Tscherne Grade	Open soft tissue injuries	Closed fractures
0		**Fr. C 0** - No or minor soft-tissue injury from a simple fracture due to indirect trauma
I	**Fr. O 1** - Skin lacerated by bone fragment. No or minimal contusion to the skin	**Fr. C 1** - Superficial contusion or abrasion to the skin
II	**Fr. O 2** - Skin laceration with circumferential skin or soft-tissue contusion and moderate contamination	**Fr. C 2** - Deep contaminated abrasions with skin or muscle contusion from direct trauma
III	**Fr. O 3** - Extensive soft-tissue damage with major vessel or nerve injury	**Fr. C 3** - Extensive skin contusion with destruction of subsutaneous tissue avulsion or muscle destruction
IV	**Fr. O 4** - Subtotal and total amputations with separation of all important anatomical structures	

The basis for this classification system was for better understanding of the velocity of the injury in traumatic fractures and its impact on the soft tissue. It took into account the kinetics of the trauma and its effect on the overlying soft tissue. Thus wounds were graded based on the severity of soft tissue involvement and surgical management could be appropriately planned depending on the grade of injury. The reported inter and intra-observer variability has been acceptable (53)

Microbiology of open wounds and antibiotic prophylaxis

Alexander Fleming was a brilliant Scottish physician, pharmacologist and biologist. He is credited for his work on bacteriology which was especially crucial during the First World War. (Fig.4).

Fig.4:- Alexander Fleming (1881-1955)



.

He condemned the use of merely using local antiseptics to treat wounds as it only reached superficial tissue and was ineffective for deeper damaged tissue and contused muscle. Most of the soldiers wounded in the battle could not be immediately attended to and lay for days in their trenches or scattered on the battlefield "no man's land" .At the same time Antoine Depage took particular interest in the study of wound management and debridement and recognized that bacterial contamination of wounds contributed to the mortality. Fleming worked alongside Depage. He tested cultures from the clothing's of 12 soldiers wounded after a battle and found that the organisms grown included Clostridium perfringens, Clostridium welchii, Clostridium tetani, streptococcus and staphylococcus species (54). He concluded that these organisms were responsible for infecting wounds and they thrived in the soil, an anaerobic environment which is where the wounded soldiers lay. Delay in treatment and cleansing of wound implied increased time for bacterial colonization (31). His major contribution however was in the field of antibiotic prophylaxis and the discovery of Penicillin in 1927.

During this time it was reported that 10% of all patients died from a killer form of gangrene known as *gangrene gazeuse* which we now know as gas gangrene. Chalier and Glenard in 1916 described 4 types of gas forming infections which were necrotising fasciitis, moist gangrene, superficial skin infections and Fournier's gangrene. The organisms responsible were Beta-hemolytic streptococci, clostridium species, anaerobic streptococci, staphylococci and other gram negative bacteria.

The use of penicillin became widespread during World War II and during the Vietnam War. Along with the advances in fracture management, triage, transport and wound care, mortality rates due to gas-gangrene were as low as 0.16% during the Vietnam War (55,56).

Staphylococcal species have been found to be most commonly encountered. As per the findings of Gustilo's prospective study in 1976, cephalosporins were considered to be the antibiotic of choice (49)

However, in their subsequent study in 1984, there was an increasing incidence of gram negative organisms. It was thereafter advocated that cephalosporins be combined with an aminoglycoside.

In 1974, Patzakis was the first to state that only 18% of infections had similar organisms from those isolated during initial wound cultures (57). This led to the introduction and growing concern of hospital acquired infections.

Later, Glass et al, at a tertiary care centre in London, evaluated a series of 52 grade 3B fractures and reported an incidence rate of 17% (58). The organisms isolated were Enterococci, Pseudomonas, Enterobacter and Methicillin Resistant Staphylococcus aureus (MRSA). These were mostly hospital acquired pathogens. The existing guidelines of antibiotic prophylaxis (cephalosporins along with an aminoglycoside like gentamycin or a beta-lactum) were found to be inadequate. They advocated use of teicoplanin along with gentamycin as a single dose blanket cover against hospital acquired and resistant organisms at the time of definite wound cover.

Recent studies have shown that antibiotic resistance and nosocomial infections is more prevalent in developed countries and the microbiologic profile of wounds varies based on the host, mechanism of injury, severity of trauma and climate involved (59). In countries high-income countries that are well developed and where cost of antibiotics is not a concern, there has been an increasing trend for development of resistant strains like extended spectrum beta lactamase (ESBL) resistant organisms, carbepenem resistant organisms (CRO) and Methicillin Resistant Staphylococcus aureus (MRSA). In contrast, developing countries like India, China, Africa and Israel, cost is the major issue and patients cannot afford second line drugs therefore high dose antibiotics are not in frequent use. Antibiotic resistance itself has been also found to be associated with increased infection risk, multiple re-admissions, and hospitalizations.

Robinson et al prospectively evaluated 89 fractures at a tertiary centre at Israel.

He stated that most wounds were contaminated at the time of revival and positive cultures obtained after more than 24 hours of debridement indicated failure in the surgery technique (60). This study highlighted the importance of the surgeon's skill and adequacy of wound debridement.

Alonge et al in his prospective series analysis of open fractures found that wounds addressed within 6 hours only isolated single culture organisms where as those debrided beyond 48 hours were positive for poly-microbial or mixed organism growth. He further proved that in over 90% cases, the organisms from superficial and deep wound cultures were the same(61).

All these studies from developing countries show that more than antibiotic prophylaxis is not the major concern in wound infections as most pathogens are sensitive to the routine antibiotics. Infections are rather dependent on the timing and methodology of wound debridement. This highlights the need for early meticulous thorough wound debridement to eliminate the infective organism is crucial.

The duration for which antibiotics need to be administered is also debatable. The British Orthopaedic Association/British Association of Plastic Reconstruction and Aesthetic Surgeons (BOA/BAPRAS) guidelines state that antibiotics should be given for atleast 24-48 for Gustilo grade I injuries. They recommend that in grade 2 and 3 injuries antibiotics must be administered for a maximum of 72 hours or till the time of soft tissue cover (10).

Surgical Debridement of wounds

As stated by Bergman(62),

"*No antibiotic can replace proper surgical management*"

Pierre-Joseph Desault along with his colleague Baron Dominique Jean Larreyare credited with naming the process of "debridement" in 1790, which was originally described as the need to extend wounds to allow for adequate free drainage. From the teachings of Hippocrates, the belief of laudable pus and suppuration to promote healing was well accepted. The necessity for surgical management of wounds only became apparent in latter 18th century with increasing number of mortalities and wound sepsis(63).

John Jones (1729–1791), also known as the Father of American Surgery promoted the need for adequate wound care during the Great American War (32). He stated that fractured limbs needed to be splinted and wounds surgically extended and excised to allow expulsion of foreign materials. He also asserted that young surgeons were inexperienced and too timid and were thus hesitant to thoroughly explore wounds. He thus defined and published treatment guidelines for the management of wounds and fractures especially for young military surgeons in North America. Much of his contribution in wound care and fracture management was through teaching and educating young doctors, the importance of which was also understood by Desault.

Pierre-Joseph Desault (1738–1795) a French anatomist and military surgeon was one of the leading surgeons of France in the 18th century. (Fig.5)

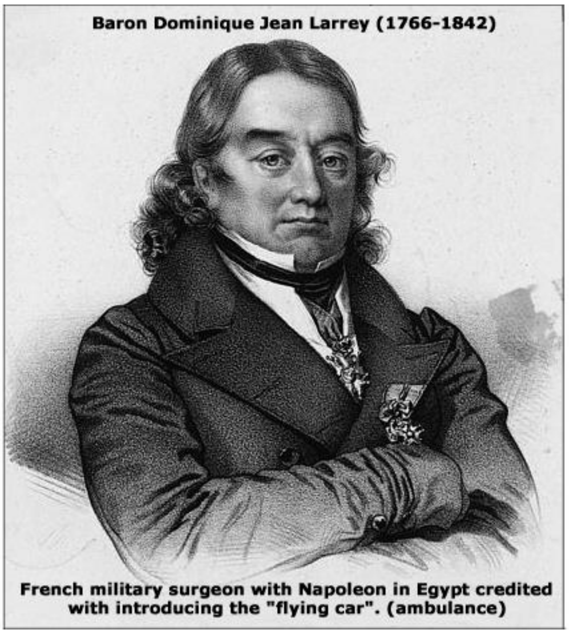
Fig.5:- Pierre-Joseph Desault (1738–1795)

He is reputed in history for his passion for teaching and improving surgical techniques in wound care. He deciphered the need for inculcating proper knowledge of anatomy in surgical practice and thereby opened a separate school for anatomy in 1766.

He observed patients at their bedside, studied and audited mortality reports and attended many conferences. He understood the importance of prompt surgical wound care, cleansing of wounds and removal of foreign bodies to accelerate healing (29). He taught numerous students about anatomy and wound management including Larrey. (Fig.6)

Baron Dominique Jean Larrey (1766–1842), a French surgeon in Napoleons army was the first to introduce the system of triage in the emergency management of open fractures(64). He was deeply saddened by the countless number of deaths he witnessed on the battlefield.

Fig.6:- Baron Dominique Jean Larrey (1766–1842)



Larrey observed that these deaths were the result of complications occurring from haemorrhage and sepsis due to a delay of upto 20 days in conducting amputations. He sought to develop a system to provide early, efficient and timely wound care. He was drawn towards the agility of the horse-artillery across the battlefield which motivated him to develop the "Flying Ambulances" system known as "ambulances volantes" in 1793 for urgent transfer of wounded soldiers(36,64,65).Larry's flying ambulances are considered the forerunners of the present-day ambulances. The triage team comprised of military officers along with medical professionals and were trained to provide immediate first aid and to instantly conduct surgeries if needed.

Larrey promoted swift transport of patients for prompt surgical wound care in horse-drawn 2 or 4 wheel carriage models. It was during this period that the terminology and concept of “debridement” in open wounds was introduced. In French the word “débrider” literally means unbridling of a horse. It referred to incising and de-tensioning of the soft tissue and fascia in wounds to unbridle or drain out unwanted foreign material and pus. It was believed that incising a wound would release pressure and reduce inflammation preventing gangrene. Bleeding was considered to be a good sign for muscle viability. Larry practised this technique to decompress soft tissue, remove debris and to also expose and ligate bleeding vessels. He recognized the importance of triage, early management of wounds and surgical debridement. In His “Memoirs of a Military Surgeon” in 1814, he stated that debridement was one of the most significant discoveries in surgery (29).

However after his death the practice of surgical management of wounds slowly lost recognition. The assumption was that surgical treatment of wounds posed a risk to soft tissue and underlying blood vessels, therefore surgeons were hesitant to incise wounds. Only open fractures with extensive soft tissue damage were managed with radical excision of soft tissue and amputations when necessary. During the American civil war, only 3% of wounds were surgically managed. The overall reported mortality was 12%.

Subsequently with the introduction of antiseptics in the latter part of the 20th century, the management of wounds changed from surgical to medical. Lister in 1867, introduced the use of carbolic acid as an antiseptic in open fractures and popularised the earlier belief of John Hunter (1728-1793) that incising wounds would result in further inflammation and were better left alone. Pilcher in 1833 advocated use of antiseptics and minimally extending wounds only if considerable soft tissue damage was anticipated in order to allow drainage and removal foreign matter. Carl Reyher (1846–1890), a Russian Army surgeon during the Franco-Prussian War, used this technique along with antiseptics in open fractures from gunshot wounds. He observed a reduction in mortality from 66% to 23%.

During World War 1, there was a change in the pattern of soft tissue injuries. Gunshot injuries were of high velocity from improved highly technical small arm artillery causing horrendous wounds with considerable soft tissue damage. Fractures of the lower limb were the most common and were reported to involve 40% of all the gunshot injuries. Further majority of the battle trenches were dug out in the soil and wounded soldiers lay there for days unattended. This led to extensive soil-contaminated wounds which facilitated colonization of anaerobic organisms. Casualties and deaths due to sepsis were florid.

The revival of the concept and introduction of the principles of surgical debridement was purely the work of Antoine Page (Fig.7) in the early 20th century (31).

Fig.7:- Antoine Depage (1862-1925)

He advocated that the surgical technique of debridement implied “excision” of wounds with extensive exploration and removal of necrotic tissue and not the earlier belief of merely “incision” of wounds to decompress tissue and fascia. He described the process of debridement in two steps which included exploration and excision and stated that the surgical incision should be planned according to the trajectory of the missile so that the foreign body along with all surrounding devitalised tissue could be excised.

He also believed in extensive and not minimally invasive incisions and that the length of the soft tissue incisions should be as long as that of the skin incision to ensure that no foreign body fragments, contused muscle or necrotic tissue was left behind. Contused muscle with impaired blood supply and oxygenation would facilitate colonization of anaerobic organisms so it needed to be removed as well.

He published the results of his technique in a study entitled *Le debridement des plaies de guerre*des in 1917. He treated 2363 wounds from May 1916 to November 1917 and reported an outstanding overall success rate of 90%. He also demonstrated that his failure rates due to infections and gangrene dropped from 11.5 to 0% in open fractures when delayed primary closure was performed. He recommended delayed closure in contaminated wounds and stated that secondary closure should be attempted only after adequate control of infections with antibiotics.

Antoine Page revolutionized the practice of military surgery and war wound management in open fractures. For his work, he was awarded the highest civilian decoration in France. Till date, adequate surgical debridement along with antibiotic prophylaxis and has evolved to be the most crucial step in the management of open fractures.

Skeletal stabilization

Restoration of bony anatomy and skeletal stabilization are the 2 crucial factors in management of open fractures (66)

External Immobilization

Immobilization of the acutely injured limb and splinting dates back to the Chinese, Egyptian and Indian civilization.

Plaster of Paris was developed by Mathijsen (1805-1878) and Pirogov (1810-1881). They found that this material conformed well to the injured limb and also facilitated in stabilization aiding both soft tissue and bony healing (44).

H. Winnett Orr (1877–1956) was an orthopaedic surgeon in the United States along with Carrel practised wound care in open fractures by cleaning wounds, packing them with petroleum-soaked gauze followed by fracture stabilization and immobilization with plaster-soaked bandages (44). This hardened by an exothermic reaction and the cast was removed at 3 weeks. Infection rates were reported to be low

The most efficient and effective splinting devices for open femoral fractures was the Thomas splint (67). It was first described by Hugh Owen Thomas in 1875. (Fig. 8) He was a Welsh surgeon and is now considered the father of Modern Orthopaedic surgery .His nephew Sir Robert Jones was appointed as a consultant orthopaedician in the British army and introduced the application of splints on the war front for wounded soldiers to stabilize both the bone and soft tissue thereby reducing pain and excessive haemorrhage in open wounds.

Fig.8: Hugh Owen Thomas (1834-1891) and Sir Robert Jones (1857-1933)

Until the start of World War 1, the mortality rates from penetrating gunshot thigh wounds and femur fractures were as high as 80%. Henry Gray, a Scottish surgeon was based in France in the initial 3 years of the First World War. During this time he observed that one of the main causes of mortality and deaths in open femur fractures were inadequate splinting of the injured limb and containment of soft tissue to organize local haemorrhage and bleeding. As a result deaths due to haemorrhage and circulatory shock were commonly witnessed both on the battlefield and during transport of wounded.

The use of Thomas splints at the war front was popularized by Henry Gray. He exclusively used these splints to immobilize all open lower limb wounds mainly gunshot wounds to the thigh during the battle of Arras in 1917. He was the first to prove the efficacy of the Thomas splint in compound ballistic injuries by demonstrating a drastic reduction in the death rates from 80 to 16% with only 17.2%

patients requiring amputations. He speculated that with universal application the Thomas splint, more lives could be increasingly saved and limbs could be salvaged. He later came to be referred to as a pioneer in the management of compound open femur fractures. The Thomas splint proved its efficacy throughout the First World War .Unqualified personnel as well were trained to apply the splint and speed of application was ensured by blind folding and training them to apply themto apply splints in succession on a series of injured patients.

However, during the Second World War in North Africa, the problem encountered was long distance transfer of wounded patients over dessert, hilly terrains and overseas in boats to seek proper medical aid. This journey proved torturous and distressing as splinting did not completely immobilize the lower limb permitting some degree of movement. Jerking of the limbs within these splints caused excruciating pain and was a harrowing experience for wounded soldiers. This led to development of the concept of traction within the splint to stabilize the long bone fracture.

In 1942, during the battle of Tobruk, the Tobruk splint was introduced and frequently used. A plaster cast was applied to the lower limb within the splint and a traction pulley was attached to the heel thus constant traction could be maintained during transfer (26).

Nevertheless, invention of the Thomas splint was a historic mark in the revolution of treatment of open lower limb fractures throughout the World Wars over the 20th century and its use in orthopaedics has been wide-spread till date. Today, with several modifications in its design and construct, it continues to be frequently used in the management of femoral shaft fractures.

<u>External fixation devices</u>

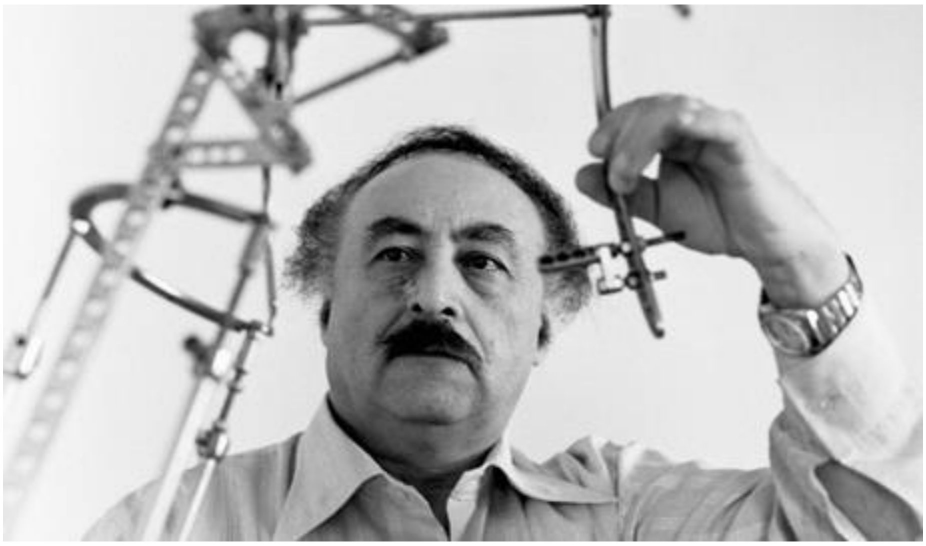
In 1840, Jean Francois Malgaigne was the first to introduce and design a modern external fixator. He first described its use in tibial fractures and the fixator point fitted into the bone like a spike and the limb was stabilized externally using straps. In 1843, he later modified this fixator point to that of a C-shaped claw clamp which had transcutaneous prongs separated by a screw. This was especially beneficial in patella fractures.In 1843 he engineered a “claw” that resembled a C-shaped clamp.

Later, in 1902, Albin Lambotte (1866–1955) also known as the pioneer of modern osteosynthesis, designed a unilateral external fixation using 2 longitudinal plates. These plates were stabilized to the sides of 4 four transverse screws. The ease of application of external fixators and better development in the design to facilitate wound care was crucial during the World War 1 which reported numerous amputations. (68).

However pin tract and later deep infections were increasingly encountered during World War 2, thus limiting the use of these fixators.

One of the biggest and successful inventions following World War 2 was the Ilizarov apparatus. Gavril Abramovich Ilizarov (Fig.9), a Russian physician was sent to the warfront without any formal training in the 1950’s.

Fig.9 Gavril Abramovich Ilizarov (1921-1992)



He was based in Kurgan, a small town in Siberia and had to manage wounds of large numbers of soldiers from World War II .Seeing the extent of soft tissue damage in open lower limb fractures and with minimal available equipment at hand, he sought to develop a fixation device to stabilize these limbs.

He likened the bicycle wheel to the cross section of a limb and worked in a cycle shop to develop a fixator construct. It was during this period that the Ilizarov ring fixator initially described for compound open fractures was invented, a device that revolutionized fracture treatment in orthopaedic surgery. The fixator initially designed had four rings. Two of these rings were fixed to the bone on both sides of the fracture by means of crossed tensioned Kirschner wires. The rings were connected wih threaded rods. This design provided good circumferential limb support.

Ilizarov’s main principles of management included adequate support of the fracture, minimize sugery, prompt weight bearing and early joint mobilization.

Fracture non-unions were addressed by compressing the rods that connected the rings. Distraction osteogenesis was discovered when a patient inadvertently lengthened the rods and callus formed in the fracture gap. Further studies resulted in the law of tension stress and a new approach to limb salvage.

The role of Ilizarov fixators in acute trauma has been proven in numerous studies. Yusuf et all in 2009 evaluated the results of acute application of the ilizarov fixator in 24 segmental tibia shaft fractures of which 17 were open fractures with predominantly grade III injuries (69). The mean time from injury to surgery was approximately 14 hours. None developed deep infections or chronic osteomyelitis and the average union time was 36.8 weeks. They concluded that the Ilizarov fixator was especially beneficial when the distal fracture segment was less than 3cm with severe soft tissue compromise.

Internal fixation devices

Hansmann in 1866, was the first to introduce internal fixation of fractures using plates (70,71). These plates were attached to the bone using screws and had long shanks that projected outside. These screws were pre-welded into the screw drivers and their handles protruded outside thus facilitating easy removal. Later, different plate designs with improvement in metallurgy and corrosion strength were introduced by Lambotte, Lane and Sherman (71). Plating of femoral fractures was first introduced during World War 1 by William Sherman. Wounds were left open for regular dressings and implants were removed at 6 to 8 weeks.

Ernest Hey Groves (1872–1944) was the first to use intramedullary rods in the treatment of lower limb fractures during World War 1 (25,32). However, the high rates of infection encountered led to its discontinuation. Küntscher however during World War II was able to successfully manage femur fractures using intramedullary nails. The widespread use of antibiotics, triage facilities and better wound management in open fractures contributed to the success of internal fixation. Tibial plates were introduced by Mc Neur during the Vietnam War and mortality rates of open femur fractures were as low as 3-4% (23).

Though Gustilo and Anderson, do not recommend internal fixation for open fractures especially in type 3 injuries (49), its use is widespread for Type 1 and 2 open tibial fractures. The reasons being, easy wound management, limb stabilization and early mobilization. In an international survey conducted by Bhandari et al in 2002 which included participation of 444 orthopaedic surgeons world-wide, it was seen that more than 88% of surgeons preferred use if intramedullary nails in Type 1 and 2 tibia fracures. However the preference rates for 3A and 3B injuries were 68% and 48% respectively.(72). This was in support of the guidelines set by Gustilo and Anderson, that external fixation was the treatment of choice in high grade injuries.

The use of reamed versus non reamed intramedullary nails is also controversial (46). The SPRINT (Study to Prospectively evaluate Reamed Intramedullary Nails in Tibial fractures) randomized controlled study evaluated 400 open fractures and evaluated the efficacy of reamed versus undreamed nails (73). All patients were followed up till a secondary re-operation procedure was performed. There was no statistically significant difference in the re-operation rates in both groups though there was a slightly increasing trend for patients in the reamed group to undergo repeated surgeries. The overall infection rate was reported to be 27%.

.

Soft tissue coverage and flaps

Complex fracture triage - "to orthopaedic traumatologist with plastic surgical support," - care is - "highly demanding, very technical and team orientated". S Hansen 1991

The ancient Egyptians were the first to understand the importance of soft tissue coverage in open wounds. The Smith Papyrus stated that ''*whenever there is a gaping wound, such as that inflicted by the mouth of a crocodile it should be covered with meat*'' (11, 23).

Baer advocated that wounds debrided within 12 hours had higher chances for success and primary wound closure based on his experience gained during World War 1. He reported a success rate of 85-90% in wounds debrided early (74). During this same period, Harold Gilles was the first to introduce flaps for soft tissue cover in infected fractures. With the large numbers of chronic osteomyelitis cases in limbs salvaged, the use of pedicle tubed flaps successfully achieved soft tissue cover in.

Marco Godina (1943-1946) was a Slovenian plastic surgeon was the first to introduce free flaps for soft tissue cover. He popularized the use of vascularized latissimus dorsi flaps. He further demonstrated that early soft tissue cover within the first 48 hours was essential for limb salvage and decreased the risk of amputations (75).

Gustilo and Anderson stated that all Type 3 injuries should have delayed wound closure either in the form of skin grafting or flaps to reduce the risk of infections (49).

Godina advocated the “fix and flap” technique in open fractures and his work has been recognized till date with reported rates of limb salvage being as high as 93% (75). The principles of wound management include antibiotic prophylaxis, thorough wound debridement, primary fixation and stabilization of the fracture followed by early flap cover.

Gopal et al in his series of 84 patients with grade 3 B Tibia shaft fractures that needed soft tissue cover, reported increased complications beyond 72 hours (76). In a retrospective analysis of 69 patients with open tibial shaft fractures requiring flaps, timing of soft tissue coverage was safe. Beyond this period the risk of complications such as wound dehisence, necrosis and infection rates increased for each day of delay beyond the 7th day (77)

<u>Timing of surgical debridement, an unresolved controversy?</u>

Paul Leopold Friedrich (Fig.10), a German military surgeon and bacteriologist pioneered the concept of primary wound closure within a definitive time frame (4). He was also known as “the founder of primary wound management”.

Fig.10 :- Paul Leopold Friedrich (1864-1916)

In 1898, Friedrich conducted a study on guinea pigs by creating an experimental wound in the triceps region and inoculating it with contaminated dust and manure. The wounds were cleaned at 30 minute intervals. He studied both the time of development of systemic infections and the effect of time delay in surgical debridement of these wounds. All guinea pigs whose wounds were debrided beyond 8.5 hours expired and those whose wounds were debrided within 6 hours survived. He also found that the early phase of bacterial growth gradually peaked to its maximum and became stationary between 6 to 8 hours. Debridement beyond this period was ineffective in completely eliminating the microorganism and preventing local spread of infection. This time period reflected the incubation time of the bacteria which was most commonly observed at 6 hours and in some cases found to be longer and even indefinite (2).

He asserted that extensive meticulous debridement within 6 hours would be beneficial in eradicating the infective organism. Debridement and use of local antiseptics after enhanced colonization or establishment of a systemic infection was futile.

Thus the origin of the 6-hour rule and timely management of open fractures, came into existence. In the preantiseptic era and uptil the culmination of World War II, wounds were left to heal by secondary intention(3,4). Invasive gas gangrene was the leading cause of mortality with death rates ranging from 8-20% (35). Introduction of antibiotics significantly decreased the incidence of infection however the amputation rates were still high.

During the First World War, William Baer described the critical time period to be 12 hours in wound management, beyond which primary closure of wounds would not be possible and complication rates would be higher (25).

In 1942, John Trueta, a British Military surgeon advocated the importance of early wound debridement and he believed that it was not the bone but the muscle that was at a greater risk for infection (4). He then instituted a 5-point programme in treating open fractures which included prompt surgery, wound cleansing, wound excision, provision of drainage, and fracture immobilization in a plaster cast (10,78).

Robson in 1973 evaluated the wounds of 80 civilians acutely injured. He reported that all wounds contaminated with > 10^5 bacterial organisms per gram of tissue before closure developed infections. Further he found that this colonization threshold peaked at an average time delay of 5.17 hours since injury (5,6).

Over the latter years of the 20th century immediate prompt transport from the battlefield, knowledge and implementation of treatment principles for open fractures, antibiotic prophylaxis, early debridement and meticulous repair of neurovascular injuries significantly reduced the incidence of major limb amputations (35). Friedrich’s 6-hour rule of early prompt debridement thereby increasingly gained acceptance as a historic standardized guideline for orthopaedicians in the management of open fractures.

Later several studies tested the validity of the 6-hour rule ;

In 1995, Kinsfater and Johansson evaluated 47 open type 2 and 3 tibia fractures and found that a time delay of > 5 hours from injury was significantly associated with development of infections (3, 79) . They also reported that deep infections and osteomyelitis did not become apparent till atleast 4.8 months post injury and positive initial culture correlation with the infecting microorganism was seen in only 25% cases. Negative cultures did not rule out the possibility of an infective sequalae. This study is important in literature as it was the first to highlight that deep infections in open fractures may remain occult in the early post-operative period and can manifest later as long as the infecting organism in the wound was inherent. This supported the findings of Friedrich’s study which showed that the incubation period of some bacteria may be longer than 6 hours and can persist locally for an indefinite period of time before the onset of systemic infections (8). Therefore both early and extensive thorough debridement of wounds play a crucial role.

Kreder and Armstrong also reported a significant difference infection rate of 25% and 12% in 56 open tibia fractures in children debrided more than and less than 6 hours from injury respectively and concluded that early wound debridement was essential (80).

In 1997, the British Orthopaedic Association (BOA) and British Association of Plastic, Reconstructive and Aesthetic Surgeons (BAPRAS) asserted that debridement of open wounds must occur early, within 6 hours of injury.

However, with the advent of antibiotic prophylaxis, numerous studies conducted in the last decade have consistently shown no beneficial role of early wound debridement within 6 hours (3,4,81–83). Given the lack of supporting evidence for early debridement, the BOA/BAPRAS group was entitled to modify their treatment guidelines in 2009 and stated that debridement upto a delay of 24 hours from injury was safe (3,4,84).

The requisite for early timely management of open fractures continues to be challenged in recent times.

Schenker et al in 2012 conducted a meta-analysis on 3539 open fractures and found no significant difference in infection rates in wounds debrided before or after 12 hours (2). In 2014, Donald Weber et al also found no difference in the overall infection rates in their series of 736 patients operated before or after 8 hours (8). However they demonstrated that tibial fractures and higher Gustilo and Anderson fracture grades (3B and 3C) had a higher predilection for developing infections. They expressed whether there was a need for early surgical debridement especially in the middle of the night considering the availability of a trauma theatre in the morning.

The same year ,PD Hull et al reported an exponential increase in the rate of deep infections of 3% for every hour of delay in debridement from the time of injury in type 2 and 3 open tibial fractures and concluded that, a delay in debridement in severe open fractures would have poorer outcomes in high grade fractures but was safe for grade 1 injuries (9).

More recently, Duyos et al in a retrospective analysis of 227 cases of open tibia shaft fractures reported that a delay in debridement beyond 24 hours was associated with an increased incidence of infection with the rates reasonably constant. This was in accordance with the BOA/BAPRAS guidelines in 2009 that debridement of wounds up to 24 hours was safe (85) .

Gopinathan et al in 2017 reported 32 cases (64%) of Type 3C open fractures in his retrospective series of 50 traumatic lower limb vascular injuries and demonstrated that the limb salvageability percentage significantly dropped from 43.2% to 16.7% in those presenting beyond 24 hours(16).

The principles of management of open fractures have thus steadily evolved over centuries and decades and have transformed one of the most dreaded and fatal injuries in war history to one which can be successfully managed with limb salvage and reconstruction. However recent literature appears to have questioned the conventional historic wisdom of early wound debridement.

METHODS

STUDY DESIGN:

We conducted a prospective cohort study over 1 year from 20^{th} October 2015 to 20^{th} October 2016.

SETTING:-

Department of Orthopaedics, Unit 1 and 3, Christian Medical College, Vellore

All adult cases of open fractures of the femur, tibia and fibula presenting to the emergency department were analysed at a tertiary care centre. We conducted a prospective cohort study from 20^{th} October 2015 to 20^{th} October 2016 after attaining approval from the Institutional Review Board. We empirically divided the cohort into 2 groups early or late based on the time to debridement (within or after 12 hours from injury).

Studies have shown that in open fractures, lower extremity is more commonly involved compared to the upper extremity, with fractures of the tibia and fibula accounting for the highest number of cases. Hence we included only lower limb open fractures in our study.

INCLUSION AND EXCLUSION CRITERIA:

INCLUSION CRITERIA

- Adult patients> 17 years with skeletal maturity (as seen on radiographs)
- All long bone open fractures of the lower limb including femur , tibia and fibula

- Patient and/or relative able to provide consent

EXCLUSION CRITERIA

- Isolated fractures involving the foot , patella, pelvis and spinal trauma
- Primary debridement/surgery done elsewhere
- Patient’s/relatives consent not obtained/unwilling to participate in the study

CALCULATION OF SAMPLE SIZE (Table 1)

Our sample size was calculated based on data from a pilot study of 50 patients and retrospective chart analysis. We calculated that a ratio of 1:5 for patients who underwent debridement within and after 12 hours respectively. The non-union rate in the early group was 20% versus 40% in the late group.

Table 1 :- Sample Size calculation (86)

Sample Size: X-Sectional, Cohort, & Randomized Clinical Trials			
Two-sided significance level(1-alpha):			95
Power(1-beta, % chance of detecting):			80
Ratio of sample size, Unexposed/Exposed:			0.2
Percent of Unexposed with Outcome:			20
Percent of Exposed with Outcome:			40
Odds Ratio:			2.7
Risk/Prevalence Ratio:			2
Risk/Prevalence difference:			20
	Kelsey	**Fleiss**	**Fleiss with CC***
Sample Size - Exposed	273	251	280
Sample Size-Non-exposed	55	51	56
Total sample size:	328	302	336

* CC = continuity correction

Results are rounded up to the nearest integer.

DATA COLLECTION

Data was obtained prospectively from all lower limb open fracture cases presenting to the emergency department and entered in the data entry proforma. Demographic variables (age , gender), comorbid conditions (smoking , alcohol consumption, diabetes, malnutrition , obesity, anaemia, respiratory disorders like asthma, chronic obstructive pulmonary disease,), mechanism of injury ,fracture location, grade, contamination, American Society of Anaesthesiology (ASA) grade, Injury severity score (ISS) ,time from injury to surgical debridement, timing and type of soft tissue coverage, type of fracture fixation and operating surgeon's years of experience were also recorded.

OUTCOMES

PRIMARY OUTCOME MEASURES:-

1) Non-union

All patients were assessed both clinically and radiologically at 9 months for union which is the maximum accepted time period for union as defined by the FDA in 1986. They stated that any fractured bone that has not completely healed within 9 months of injury and that has not shown radiographic progression towards healing over 3 consecutive months on serial radiographs should be considered as a non-union.

Radiographically, a non-union was defined by the presence of the following criteria: - absence of bone trabeculae crossing the fracture site, sclerotic fracture edges, persistent fracture lines, healing of less than 3 out of 4 cortices and lack of progressive change towards union on serial radiographs(87–89).

Clinically persistent pain at the fracture site, inability to full weight bear on the injured limb, pain on palpation or on weight bearing and abnormal mobility was also assessed to help aid the diagnosis (90)

SECONDARY OUTCOME MEASURES

1) <u>Infections</u>

We defined deep infections by:-

All wounds requiring an unplanned surgical debridement and/or sustained antibiotic therapy following definitive closure, excluding any pin tract infections(7–9).

Wound healing was evaluated by examining the wound to determine if it was ideally, acceptably or minimally healed (91).

An ideally healed wound – results in return to normal anatomic structures, function and appearance that include a fully differentiated and organised dermis and epidermis with intact barrier function.

An acceptably healed wound – characterized by epithelisation capable of sustaining functional integrity during activities of daily living.

A minimally healed wound – characterized by restoration of epithelial coverage that does not establish a sustained functional result and may recur.

We considered a time limit of 1 month post injury to assess wound healing as chronic non-healing wounds are considered to have entered a state of pathological inflammation due to subclinical infection or formation of biofilms by the bacteria and have a higher predilection of becoming infective (55,92).

We also considered assessment of the CRP marker in the blood at 1 month

Studies have shown that CRP levels help in the diagnosis of infections after open fractures if they are not clinically evident(93).

2) Secondary surgical procedures, complications, health care expenditure:-

The number secondary surgical procedures, re-admissions, duration of hospital were also recorded over 9 months. All inpatient bills were analysed to assess the cost of direct health care expenditure.

3) Functional outcome:-

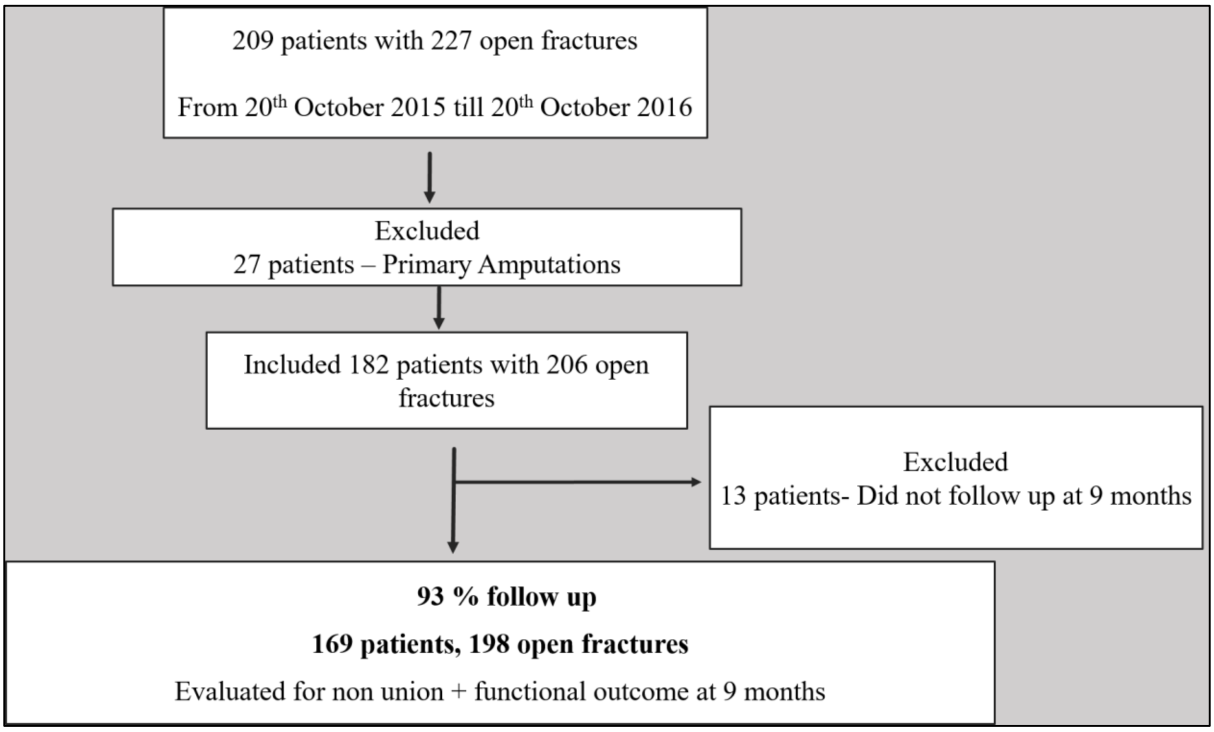
Functional outcome was assessed by determining whether patients had returned to work at 9 months and by health based questionnaire scoring systems [short musculoskeletal functional assessment (SMFA) and Short form -36 (SF-36) scores]

The SMFA scoring system as described by Swiontkowski et al is a two-part, 46-item, self-reported health-status questionnaire(11,46,94). One part, the Dysfunction Index, is designed to detect differences in the functional status of patients who have a broad range of musculoskeletal disorders that are commonly seen in community practices. The second part, the Bothersome Index, allows patients to evaluate how bothered they are by functional problems. Both Short Musculoskeletal Function Assessment indexes are scored from 0 to 100 and higher scores indicate poorer function

The SF-36 scoring system is a widely accepted, well-validated functional status measure that was developed from the Medical Outcomes Study(12).It is a self-administered, 36-item questionnaire that measures health-related quality of life in eight domains that can be aggregated into a physical and a mental summary score. Each summary score is scored separately from 0 to 100, and lower scores indicate poorer function.

A flow chart of the number of patients recruited in the study is shown below. (Fig.11)

Fig.11:- Flow chart of the patients recruited



There were a total of 209 patients with 227 open long bone fractures of the lower limb that presented to the emergency department from 20th October 2015 to 20th October 2016. 27 patients who underwent amputations were excluded. We recruited a total of 182 patient with 206 open fractures and had a 93% follow up rate at 9 months.

169 patients with 198 fractures were analysed at 9 months.

STATISTICAL ANALYSIS

Data was entered using Microsoft Excel 2016. Discrete variables like age, sex, co morbidities and fracture grade were evaluated using independent 2 sample t tests and continuous variables like time by chi square tests. Multivariable logistic regression was used with probability of non-unions as the primary outcome Time was also primarily analysed as a continuous variable in the model to determine the additive effect of delay without arbitrary cut-off thresholds. A p value of less than 0.05 was considered significant.

RESULTS

The patient demographics and fracture characteristics were as follows. (**Table 2**)

Table 2. Patient and fracture characteristics

Variable	
Mean Age(years) (range)	41.15 (17-77)
Sex (n, %) - Male -Female	 145 (73.2%) 24 (26.8%)
MOA* (n, %) RTA * Crush injury Fall	 159 (94.1%) 6 (3.5%) 4 (2.4%)
Gross Contamination %	129 (65.1%)
Median ASA*score (range)	1 (1-5)
Median ISS* score (range)	11 (6-34)
Median Time to debridement (hrs*)(range) Mean Time to antibiotics (hrs)(range) Fracture grade % - 3A - 3B - 3C Operating surgeon % - Consultant - Registrar Fixation device (n, %) No fixation External fixation Internal fixation Mean serum CRP (mg/dl) (range) Deep infection rate (n, %)	15.6 (4.5-164) 9.6 (1.4-122.4) 61 (30.8%) 130 (65.6%) 7 (3.6%) 118 (69.8%) 51 (30.2%) 9 (4.6%) 44 (22.2%) 140 (73.2%) 22.7 (3.14-201) 71 (35.6%)
Nonunion rate (n, %)	63 (33.5%)

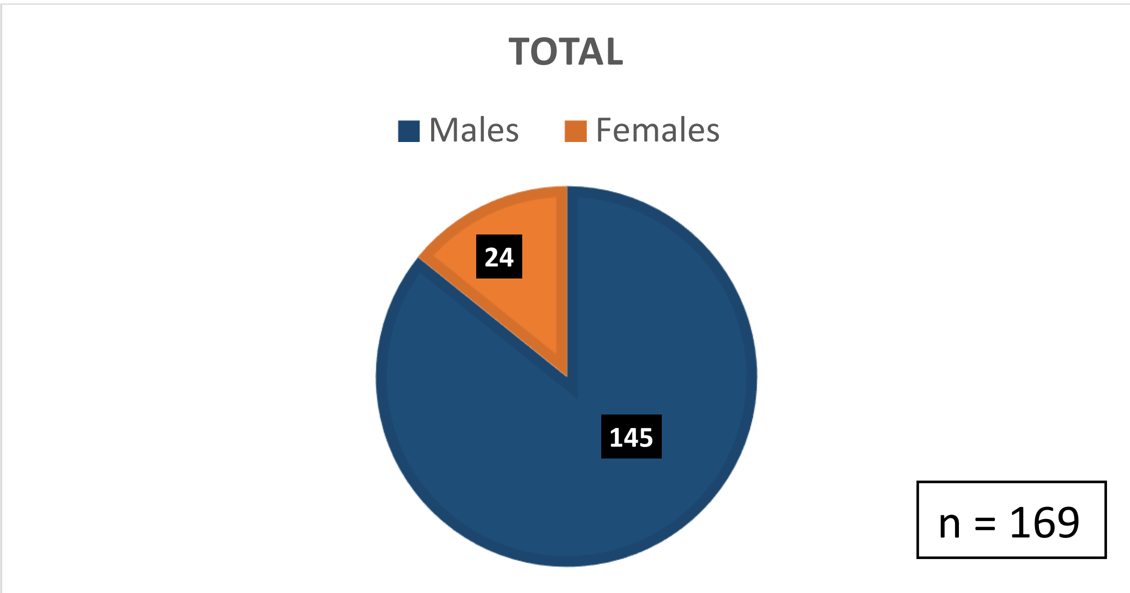
*MOA-Mechanism of accident, RTA-Road traffic accident, ASA- American Society of Anaesthesiology classification, ISS- Injury Severity Score, hrs – hours

We analysed a total of 169 patients with a 198 open fractures involving the lower limb which included femur fractures, tibia/fibula inclusive of intra-articular fractures and those involving the ankle mortise.

There were 42 patients with a total of 54 fractures who underwent debridement within 12 hours and a total of 127 patients with 144 fractures in whom surgical debridement was done beyond 12 hours of injury. The mean age of the patients were 41.5 years (17-77), with majority being males **(**Fig.12a)

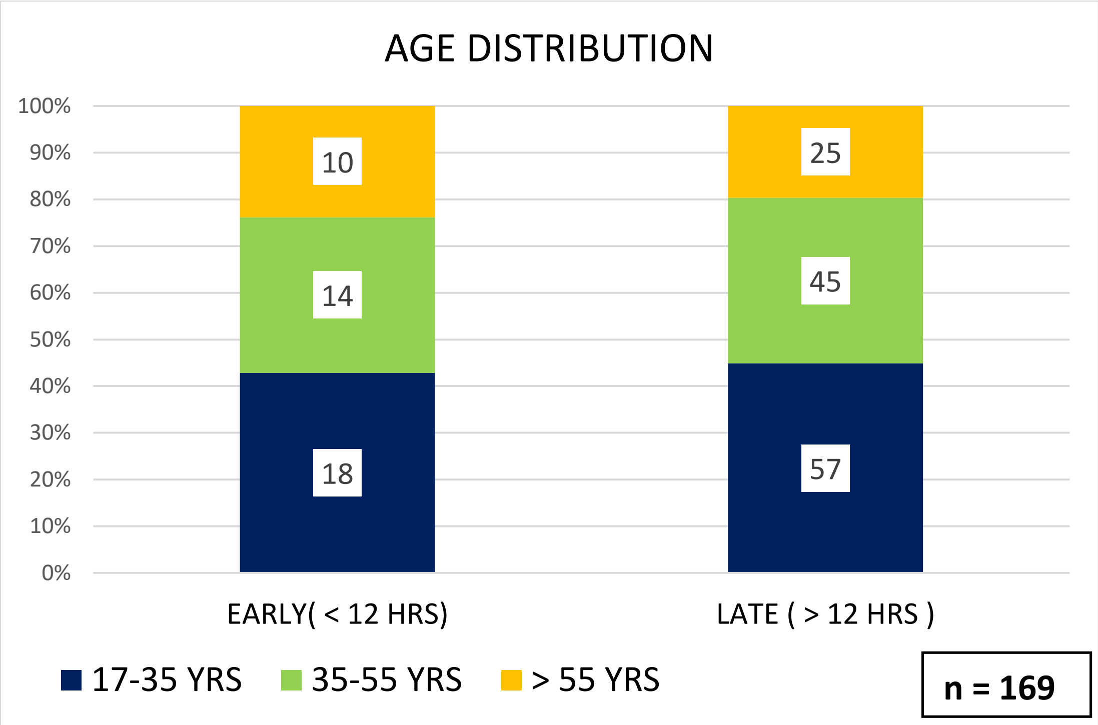
145 of the patients were males (86%) and the remaining 14% were females.

Fig.12a:- Patient age distribution



The age-wise distribution of patients in both the early and late groups is shown below. (Fig.12b).

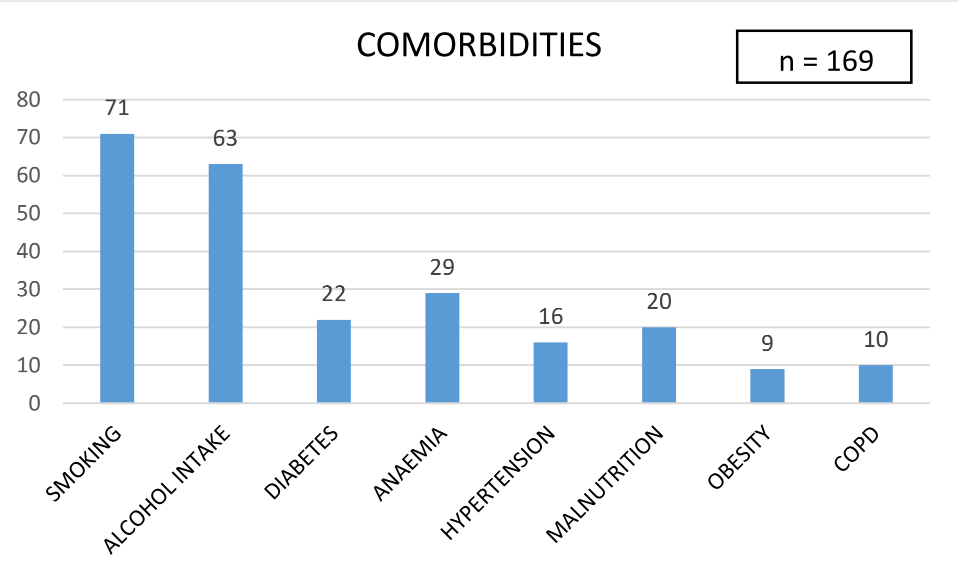
Fig.12b:- Percentage age-wise distribution (Early versus late group patients)



Both groups comprised of patients predominantly in the younger age group.

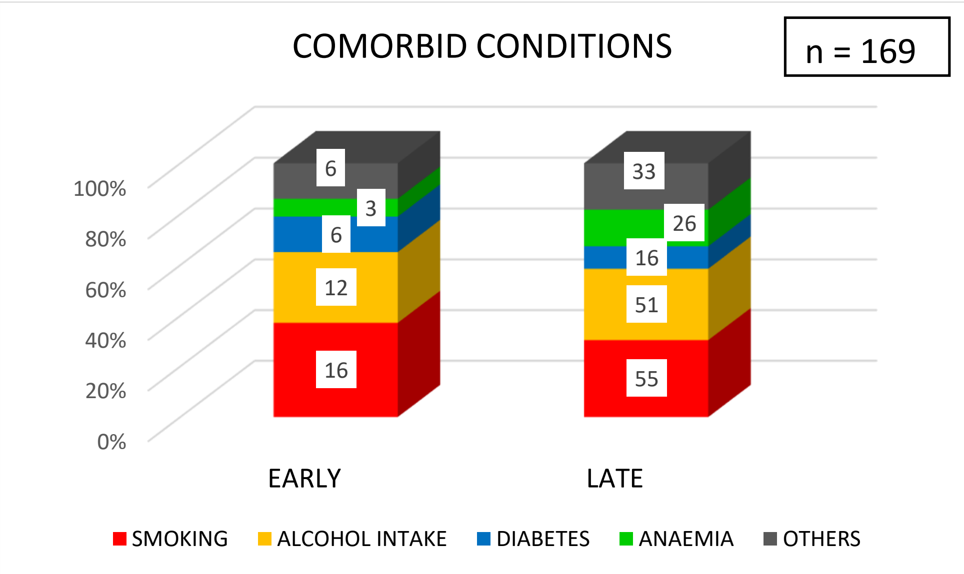
The distribution of the patient co morbidities which included smoking, alcohol intake, diabetes mellitus, hypertension, malnutrition, obesity, anaemia and COPD (chronic obstructive pulmonary disease) is as shown in Fig.13a.

Fig.13a:-Patient co-morbidities



A comparison of the patient co morbidities in both the early and late groups is depicted below. (Fig.13b).

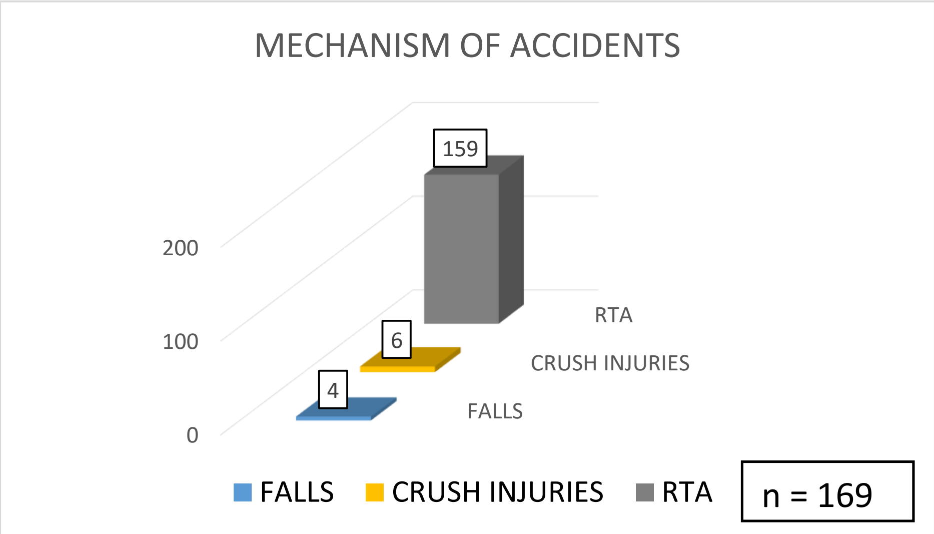
Fig.13b:- Patient co-morbidities :- (Early versus late group)



Smokers were predominant in both the groups and comprised of 38% and 43% of the patients in the early and late group respectively.

Fig.14 shows the mechanism of trauma etiology.

Fig.14:- Mechanism of trauma

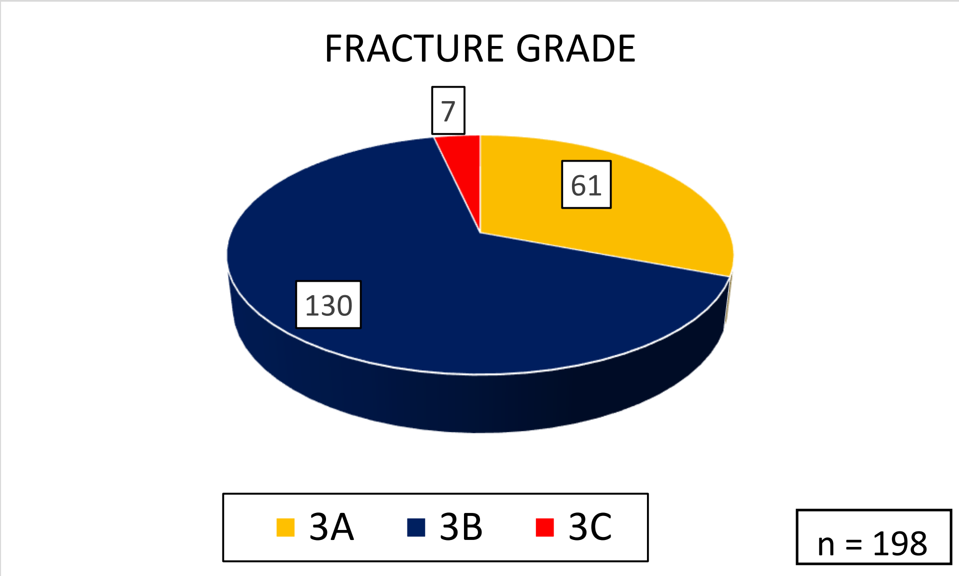


Most of the injuries were due to road traffic accidents which was seen in 159 patients (94.8%) and the remaining were due to crush injuries or falls.

Most of the wounds were grossly contaminated on arrival (65%). The median ASA and ISS scores were 1 (1-5) and 11 (6-34) respectively.

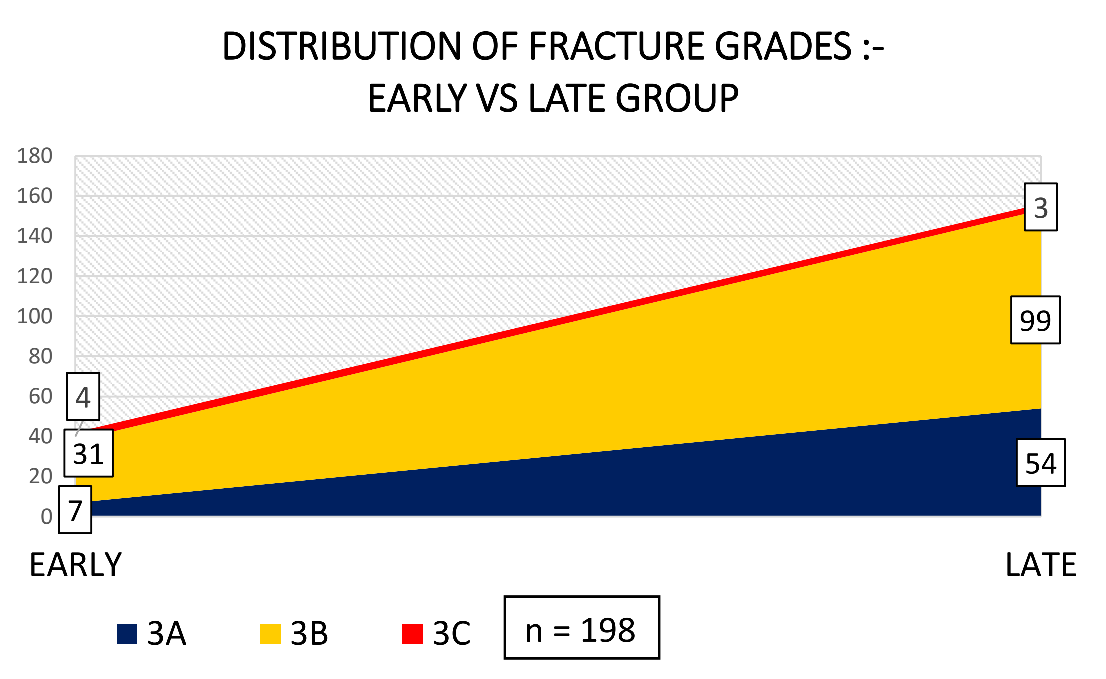
The overall median time to debridement was 15.6 hours (4.5-164). The mean time to antibiotic administration was 9.6 hours (1.4-122.4) (Table 1). The fracture grading was as **follows. (Fig.15a).**

Fig.15a:- Gustilo and Anderson Fracture grade (198 open fractures)



All fractures were high grade injuries (Gustilo and Anderson grade 3 type) with 3B being the most common. Out of a total of 198 fractures, 130 were 3B type (65.6%), 61 were 3A (35.6%) and the remaining 7 fractures were of 3C grade (3.5%). Comparison of the fracture grade distribution between the Early and Late groups is shown in Fig.15b.

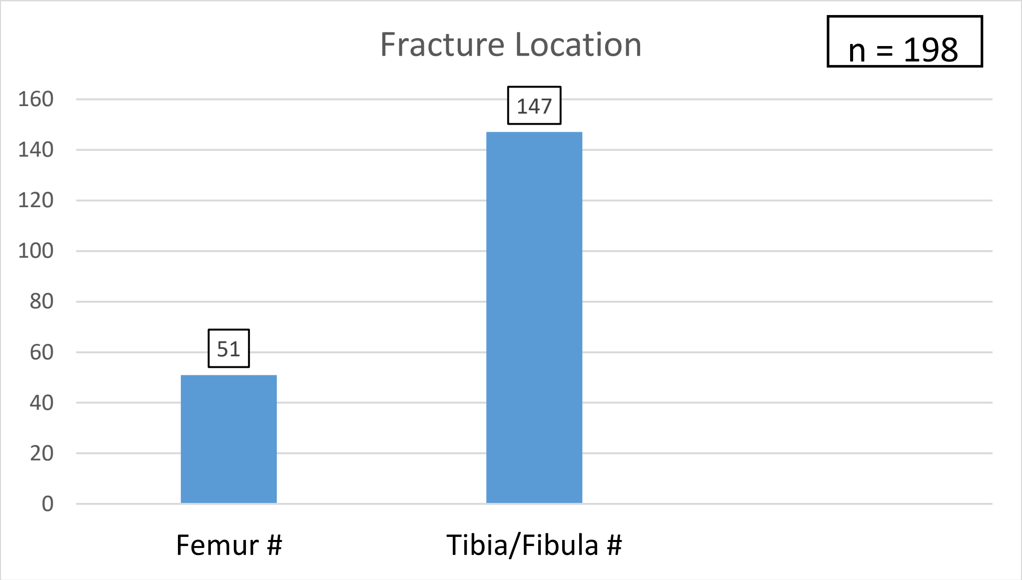
Fig.15b:- Fracture Grade – (Early versus Late group fractures)



3B injuries were predominant in both groups with a total of 99 patients in the late group (68.8%) and 31 patients in the early group (57.4%). The early group had a significantly lower number of 3A fractures as compared to the late group (7 versus 54). The late group comprised of 88.5% of all the 3A fractures. The remaining 7 fractures were grade 3C, 4 of which underwent early and 3 late debridement.

The distribution of the site of fracture involvement (femur, tibia/fibula) is shown in Fig.16. The group of fractures involving the ankle mortise included isolated fibula – lateral malleolus or distal 1/3rd fractures which were fixed or those involving the tibial pilon or medial malleolus.

Fig.16:- Fracture Location (Femur versus leg (Tibia/Fibula)

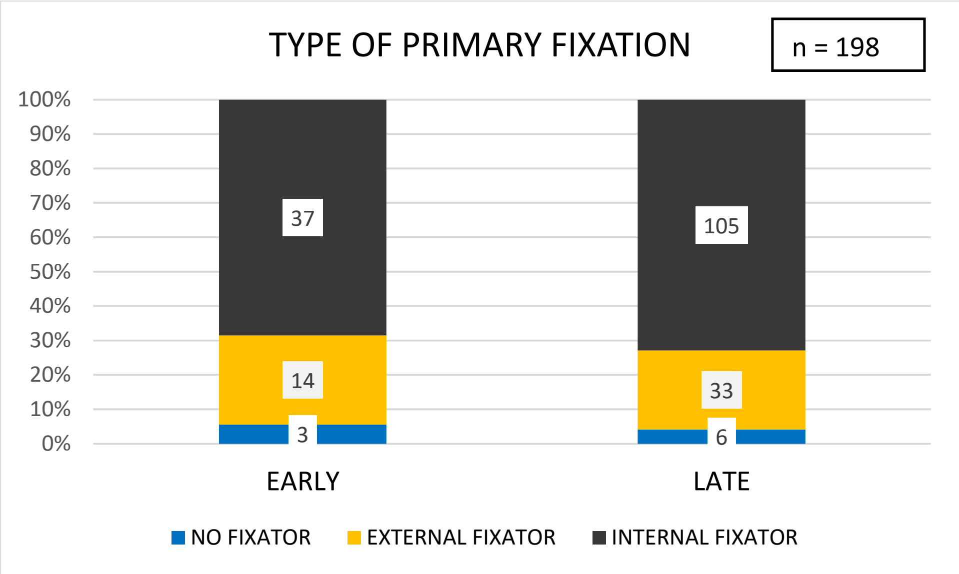


Majority of the fractures involved those of the tibia/fibula which accounted for 74.2% of the total fractures followed by fractures involving the femur shaft (25.8%). These were inclusive of intra-articular fractures.

Debridement was done by a consultant in 70% patients (Table 2).

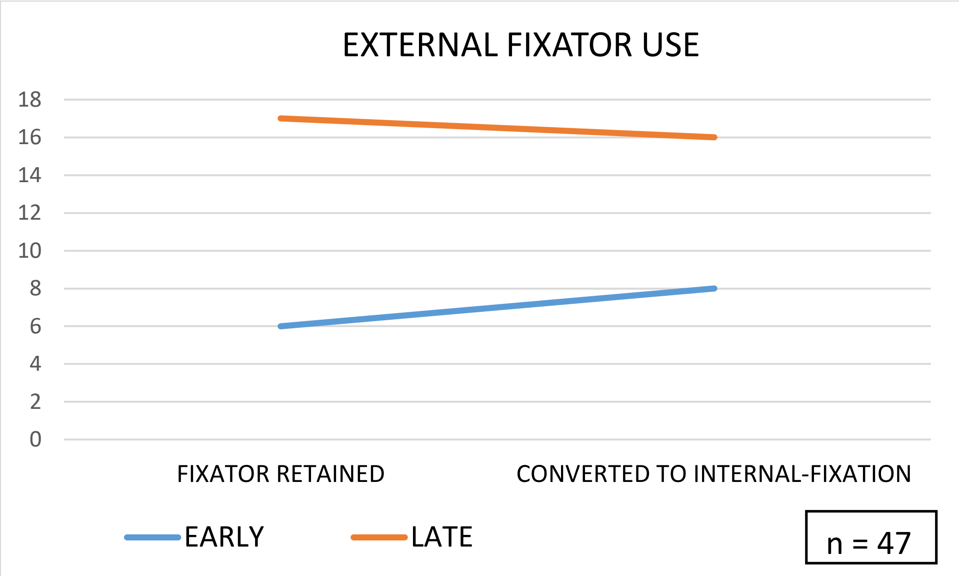
Regarding the choice of fixator device used, internal fixators were most commonly used primarily. 71.7% fractures were fixed primarily using an internal fixator device which included intramedullary nailing, plate or screw fixation. The remaining fractures were stabilized primarily with an external fixator that included uniaxial external or ring fixators. A comparison between both groups of patients and type of primary fixation done is shown in Fig.17.

Fig 17:- Type of primary fixation (Early versus late group fractures)



The use of primary internal fixation was predominant in both groups of patients and comprised of 68.5% and 72.9% of the fractures in the early and late group respectively. 4 patients underwent change of fixation from external to internal fixation (3 in the early and 1 in the late group) as shown in Fig 18.

Fig.18 :- External fixation (Early versus late group fractures)



2 patients in the late group required conversion from internal to an external fixator device.

In majority of the patients skin cover in the form of primary closure, flaps or skin grafting was done early (within 7 days). Primary closure was done most commonly in both groups. A comparison of the type of wound closure in the early and late group is shown in Table 3.

Table 3:- Type of wound closure (Early group versus late group fractures)

Wound closure	Early group (n = 54)	Late group (n = 144)	p-value
Primary closure (n, %)	36 (66.6%)	89 (61.8%)	0.5
Flaps (n, %)	**16 (29.6%)**	**24 (16.6%)**	**0.04**
STSG (n, %)	**2 (3.7%)**	**31 (21.6%)**	**0.003**

In both groups of patients, primary closure of the wound was predominantly performed at the time of initial surgical debridement (66.6% versus 61.8% in the early and late group respectively). However the number of flaps done was more in the early group, 29.6% of the patients as opposed to 16.6% in the late group. This is probably due to the fact that many of the patients in the early group had large soft tissue defects and appeared to present earlier than those in the late group. Presence of large soft tissue defects with skin loss made this group of patients more likely for aggressive management and intervention, with early soft tissue cover. The comparison of the number of flaps done in both groups of patients was statistically significant. The late group of patients also had a significantly larger number of patients that underwent secondary skin grafting (21% as compared to 3.7% in the early group). Most of these procedures were done on secondary basis due to wound necrosis and breakdown following primary closure.

Our primary outcome was to study the effect of time to initial surgical debridement on the development of non-unions in open long bone fractures of the lower limb. The overall incidence of non-unions at 9 months was 35.3%. There were a total of 63 non unions. 3 patients expired and 7 underwent an amputation before 9 months due to deep infections. All these patients belonged to the late group and were excluded in the analysis for non-unions. The unadjusted analysis of the predictors for non-union in open fractures is depicted in Table 4.

Table 4:- Predictors for non-union (Total 188 fractures)

Variable	Union (n = 125 fractures)	Non-union (n = 63 fractures)	p- value
Mean age (years)(range)	39.8 (17-73)	42.3 (17-77)	0.3
Male sex (n, %)	106 (84.8 %)	53 (84.1%)	0.9
Smoking (n, %)	48 (38.4%)	32 (50.8%)	0.1
Alcohol intake (n, %)	42 (33.6%)	29 (46%)	0.09
High Gustilo grade 3B/3C (n, %)	79 (63.2%)	48 (76%)	0.08
Tibia fractures (n, %)	75 (60%)	42 (66.6%)	0.3
Gross contamination (n, %)	83 (66.4%)	46 (73%)	0.36
Mean Mess score (range)	3.2 (0-7)	2.9 (0-7)	0.7
ASA score > 3 (n, %)	8 (6.4%)	4 (6.3%)	0.9
ISS score > 25 (n, %)	27 (21.6%)	11 (17.5%)	0.5
Surgeon's experience Consultant (n, %)	89 (71.2%)	46 (73%)	0.79
Mean time to debridement (hours)	**18.3 (4.5-120)**	**31.3 (4.5-164.3)**	**0.0001**
Mean time to antibiotics	8.8 (1.4-100.4)	7.2 (4.2-122.5)	0.4
Internal fixation (n, %)	93 (74.4%)	44 (69.8%)	0.3
Type of wound closure Primary (n, %) Flaps % (n, %) Delayed/STSG (n, %)	87 (69.6%) 25 (22.4%) **13 (10.4%)**	37 (58.7%) 12 (19%) **14 (22.2%)**	0.1 0.6 **0.03**
Wounds not healed at 1 month	**47 (37.6%)**	**47 (74.6%)**	**0.0001**
CRP > 6mg/dl at 1 month	**47 (37.6%)**	**37 (58.7%)**	**0.006**
Deep infection (n, %)	**31 (24.8%)**	**35 (55.5%)**	**0.0001**

We found that baseline characterics like age, male gender, smoking, alcohol intake, wound contamination, tibia shaft fracture, higher Gustilo grade, ASA, ISS scoring, primary experience of the operating surgeon (consultant or registrar), time to antibiotic administration, primary wound closure, flaps and use of primary internal fixation did not have any significant co-relation with the development of non-unions. Further even though the overall percentage of smokers was slightly higher in those that had a non union (50.8% versus 38.4%), it was not statistically significant. The median time to debridement was 14.5 hours and the mean time 18.3 hours in those whose fractures united as compared to a median time of 20.5 hours and mean time 31.3 hours in the non union group. This difference was statistically significant (p = 0.0001). Delayed wound closure with skin grafting was also shown to be associated with non union. (p = 0.02). The other significant predictors for non union were a CRP value more than 6mg/dl (p = 0.006) and wounds that did not heal at 1 month (p = 0.0001). Deep infections were also significantly associated with non unions (p = 0.0001).

The non-union odds ratio risk for the late group is shown in Table 5.

Table 5:- Non-union and infection rates –Odds ratio risk for debridement > 12 hours

Variable	Odds ratio	p-value
Non-union	6.94 (2.52-19.12)	<**0.001**
Infection	7.49 (2.62-21.39)	<**0.001**

. The non-union rate in the late group was 4.6 times higher as compared to the early group (42.5% versus 9.2%) .

Statistical analysis for multivariate regression analysis for non-union was performed in three parts. First, we assessed whether rates of non-union were significantly different between the two study groups (early and late). Adjusting for correlation among fractures within single patients, we found a significant difference in the non-union rates between the early and late groups (Crude Odds ratio= 6.94, P<0.001). (Table 5)

Secondly, we tested for differences in baseline socio-demographic and clinical characteristics between the two study groups. Presence of anaemia, ASA score above 2, higher levels of CRP (more than 6mg/dl), presence of wound healing, grade 3B/3C fractures contamination, infection, late wound cover and type of fracture were associated with timing of debridement.

Thirdly, to account for these baseline differences between study groups, a multivariable logistic regression analysis was performed using the method of generalized estimating equations. After adjusting for factors found to be different in the uni-variable analysis, a delay of more than 12 hours was found to be an independent predictor of non-union in the multi-variable analysis (Adjusted Odds Ratio = 5.89, p <0.001). (Table 6)

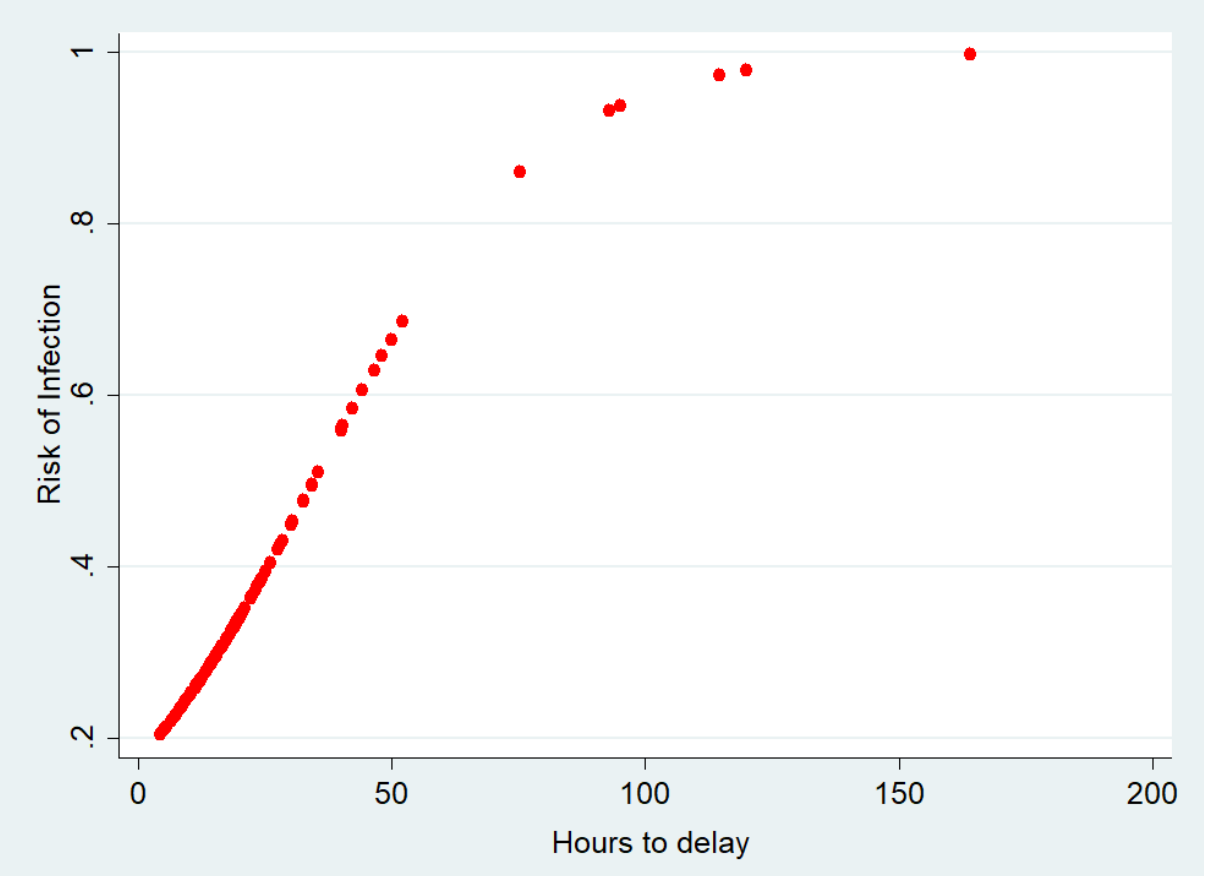
Table 6:- Multivariable regression analysis, Primary outcome: Non-union

Variables	OR	95% CI	p - value
Time to debridement (> 12 hours)	**5.89**	**(1.72,20.13)**	**0.005**
Anaemia	1.14	(0.45,2.87)	0.781
ASA grade > 2	1.18	(0.52,2.71)	0.693
CRP > 6mg/dl	0.99	(0.983,1.00)	0.172
Wounds not healed at 1 month	0.479	(0.19,1.20)	0.119
Higher Fracture grade – 3B/3C	2.41	(0.986,5.92)	0.054
Gross contamination	1.01	(0.41,2.51)	0.977
Deep	2.22	(0.89,5.51)	0.085
Late wound cover	0.641	(0.23,1.77)	0.393
Tibial fracture	1.48	(0.75,0.295)	0.258

Our secondary outcome measure was to study whether late debridement had an increased predilection for infections. We only considered the deep infections in our analysis. We found that the infection rates in the late group were 6 times higher than the early group (46.5% versus 7.4%). The odds ratio risk for development of infections in the late group was 7.49. (Table 5)

The association between time to debridement and the overall infection risk is shown in Fig.19.

Fig.19:- Odds of increase in infection risk for each hour of debridement



Analysing the time to debridement as a continuous variable, we found that there was a 6 % increase in the infection risk for each hour of surgical delay from the time of injury. This had a linear relationship upto the initial 50 hours. (OR 1.06, 95% CI, 1.02-1.07) ($p < 0.0001$).

We also assessed wound healing and analysed CRP levels at the end of 1 month. As shown in Table 1, CRP levels > 6mg/dl were significantly associated with development of non-unions at the end of 6 months. A comparison between the CRP levels and wound healing in the early and late group is shown in Table 7.

Table 7:- Mean CRP and wound healing at 1 month in early versus late group fractures (198 fractures)

Variable	Early group (n = 54)	Late group (n = 144)	p-value
Mean CRP (mg/dl) (range)	7.6 (3.14-12)	28.4 (3.14 - 201)	**<0.0001**
Wound healing at 1 month (n, %)	48 (88.9%)	46 (32.4%)	**<0.0001**

Thus the patients who underwent debridement early, had significantly lower serum CRP levels at 1 month. Further all wounds had healed in 88.9% patients in the early group at the end of 1 month which was almost 3 times that of the late group.

The differences in both the early and late group with respect to the average number of additional surgeries per patient, mean number of readmissions per patient, in-patient bill per patient, number of major complications and return to work at the end of 9 months is shown below in Table 8.

Table 8:- Outcome analysis of 9 month follow up (Early versus late group patients)

Variable	Early group (n = 42)	Late group (n = 127)	p-value
Mean No. of readmissions/patient	**0.4** (0 – 3)	**0.8** (0 – 5)	**<0.001**
Mean length of stay	13.9 (3 – 54)	16.2 (5 – 50)	0.3
Mean No. of additional surgeries/patient	0.64 (0 – 3)	1 (0 – 6)	0.6
Mean Cost (in patient bill)/patient (lakhs)	1.38 (0.52-4.6)	1.67 (0.56 – 4.8)	0.4
Major complications (n, %) - Amputations - Deaths	0 **(0%)** 0 0	7 (**5.5%)** 5 3	**<0.0001**
Return to work % (n)	35 **(83.3** %)	43 **(34.7** %)	**<0.0001**

There was no difference in the overall length of hospital stay, mean total cost per patient and number of additional surgeries required in both the early and late groups. The detailed analysis and comparison of the type of additional surgeries performed in both the early and late groups is shown in Table 9.

Table 9:- Additional surgeries performed (Early versus late group patients)

Surgery Type	Early group (n = 27)	Late group (n = 127)	p-value
Wound debridement (n, %)	**4 (14.9)**	**58 (45.7%)**	**0.0004**
Redo-fixation (n, %)	**11 (40.7%)**	**21 (16.5%)**	**0.001**
Bone grafting +/- Redo fixation (n, %)	6 (22.2%)	17 (13.4%)	0.2
Soft tissue procedures (n, %)	6 (22.2%)	31 (24.4%)	0.8

The additional surgeries done in the early group were predominantly conversions from temporary external fixation to definitive fixation, whereas those in the late group were unplanned wound debridement procedures for infections. Both these differences were statistically significant. There was no difference in the number of patients that underwent bone grafting, with or without redo-fixation in both groups. The soft tissue procedures included vascular repairs, flaps, skin grafting and amputations which were comparable in both groups of patients.

The functional outcome scoring assessment using the SMFA and SF-36 PCS was only done for patients whose fractures had united at the end of 9 months. 90 patients had united lower limb fractures. We excluded 7 patients who had severe head injuries. The results were as follows.(Table 10).

Table 10: **-** Comparison of the mean SMFA and SF-36 PCS scores between the early and late group patients with united fractures at 9 months (83 fractures)

Functional score	Early group (n = 35)	Late group (n = 48)	p-value
Mean SMFA- (DI + BI) score*	**44.3** (9.2 - 65.4)	**72.4** (11.5-88.4)	< **0.0001**
Mean SF-36 PCS score *	**59.7** (34.2 - 92.9)	**21** (32.3-88.9)	< **0.05**

*DI – Dysfunction index, BI- Bothersome index, PCS – Physical component score

The early group had a superior functional outcome as compared to the late group, this appeared to be probably due to the fact that many of the late group patients had minor complications like knee and ankle joint pain with stiffness. This was seen in 40% patients in the late group as opposed to 10% in the early group. These complications may have occurred as a result of infections which was significantly higher in the late group. (Table 5)

DISCUSSION

Historically, open fractures were associated with high morbidity and mortality. Along with the discovery of antibiotics and principles of wound debridement that were applied in World War 1, the mortality of lower limb fractures due to infections and gas gangrene reduced drastically from 20 to 0.16% (31). Advances in technology, better understanding of pathophysiology and availability of complex reconstructive procedures made good outcome possible even in previously unsalvageable limbs.

A major reason for the good results mentioned above was thought to be due to early debridement. This line of thinking has been challenged lately. Recent studies have shown no apparent association between time and development of infectious complications in open fractures. However all these studies were conducted in the West, where the setting of these injuries is completely different.

In our setting, the lack of protective clothing worn by motorcyclists combined with dirty roads predispose the injured lower limb to much higher degrees of contamination leading to infections. Further, the hot tropical climate conditions provides a favourable medium for colonization of bacteria. Moreover, the percentage of open fractures appear to be higher in our country as also the mechanism of injury being motor vehicle accidents. We hypothesized that late debridement as advocated in Western literature, if applied in our condition would significantly affect union and infection rates in open fractures.

Most of the Western literature deals with infection rates in open fractures. Westgeest reported a non-union rate of 17% in a prospective analysis of 736 open fractures (95). However their follow-up time was longer. They used telephonic interviews and clinical records for analysing non-union. They further reported a 13% discrepancy in patient and surgeon described outcomes as to whether the fracture had healed or not. Hence, the data used for analysis may have been incomplete. The overall non-union rate observed in our study was 33.5%. We had a 93% follow up rate which was comparable with that of Westgeest study (94%). Our methodology used to assess non-union seemed more accurate as it was done using both clinical and radiological parameters prospectively.

Studies from the West have stated that the mechanism of trauma in open fractures was predominantly due to low velocity falls or crush injuries (42,47). Type 1 and 2 Gustilo grade fractures are predominant in most of the studies from the West. Lower limb fractures with involvement of the tibia/fibula , gross contamination of the wound and high grade fractures (Gustilo grade 3B/3C) have been found to be significantly associated with infections (8,9). The overall infection rates varied between 10-15% in all these studies. Time to surgical debridement has no influence on the infection rates in these studies. However, except for the prospective study conducted by Weber et al in 2014 on 736 open fractures (8), all the other studies were retrospective in nature (7,9,79). Further most of them included open fractures of the upper limb as well, thus comparison between different patients would have been limited by the difference in behaviour of upper and lower limb fractures.

We reported an overall deep infection rate of 35.6% and a 6% increase in the infection risk for each hour of surgical delay. The study with similar results to our study was the one conducted by Hull et al in 2014 which showed a 3% increase in the infection risk for each hour of surgical delay in Grade 2 and 3 injuries. This was a retrospective study and included fractures of the upper limb and feet as well (9).

Pollak et al, in a prospective study on 315 grade 3 lower limb fractures reported infection rates as high as 27%, which was comparable to our study (96). They also included foot injuries. Superficial infections including pin tract infections and cellulitis were taken into account as well. However, they found no association between time to debridement and infections. Duyos et al also reported the same infection rates in a retrospective analysis of 227 tibial fractures (85). However all patients in his series underwent debridement beyond 24 hours which may have accounted for the higher infection rates.

The strengths of our study included the prospective nature. We only included long bone lower limb fractures to ease in comparison between patients. Further, fracture union was confirmed only by a group of senior consultants at the end of 9 months who were blinded as to whether the patient belonged to the early or late group. This excluded single observer bias. Finally, our study assessed the functional outcome of all these patients at the time of follow-up. It was observed that a significantly higher percentage of patients in the early group had returned to work at 9 months compared to the late group. This was of particular importance in our setting, considering that the majority of patients were males and soul breadwinners of the family. We also found that in the united fractures, the functional scoring of patients in the early group were significantly higher. This showed that even in the fractures which healed in the late group, pain and stiffness caused by the consequences of delayed debridement had a bearing on functional outcome. This was in agreement with our hypothesis, that time to debridement had a profound impact on the overall quality of life as well. This study also pointed out the dangers of applying conclusions based on studies in the West without taking the local conditions into account.

LIMITATIONS

Our study was limited by analysis of all patients only at 9 months for non-union. Thus all patients were not followed up till fracture union. However considering the maximum accepted FDA criteria period of 9 months for non-union, this time period seemed reasonable.

Since our hospital is a multispecialty tertiary care centre with a large number of referral patients, the exact time of antibiotic administration was not available for all patients who received the first dose elsewhere. Studies have demonstrated that early administration of antibiotics in open fractures reduces the infection rates (57, 62, 82). The timing of dosage for these patients was taken as the time at which they were administered at our hospital. However there was no significant difference in the antibiotic timing while comparing between the fractures that united and those that did not. Further this variable was not accounted for in the multivariate regression analysis for non-union as the timing of antibiotic administration was comparable in the early and late groups (Table 4 and 6).

Further we only took into account the overall in-patient hospital bill for cost did not take into account the individual pharmaceutical drug expenditure in the direct cost analysis. Considering that a larger number of patients in the late group had not returned to work at 9 months (83.3%) (Table 8), An indirect cost assessment analysis including transportation may have considerably added to the socio-economic impact of late debridement.

CONCLUSION

Our study conclusively proves that debridement in open fractures should be done as soon as possible. This is particularly of importance in developing countries which bear the brunt of trauma. Formulating protocols for early wound management may be beneficial in saving life, limb and money.

REFERENCES

1. Kim PH, Leopold SS. Gustilo-Anderson Classification. Clin Orthop. 2012 Nov;470(11):3270–4.

2. Peltier LF. Fractures: A History and Iconography of Their Treatment. Norman Publishing; 1990. 314 p.

3. Azar FM, Calandruccio JH, Grear BJ, Mauck BM, Sawyer JR, Toy PC, et al. Controversies in Fracture Care, An Issue of Orthopedic Clinics, E-Book. Elsevier Health Sciences; 2016. 137 p.

4. Rozell JC, Connolly KP, Mehta S. Timing of Operative Debridement in Open Fractures. Orthop Clin North Am. 2017 Jan;48(1):25–34.

5. Robson MC, Duke WF, Krizek TJ. Rapid bacterial screening in the treatment of civilian wounds. J Surg Res. 1973 May 1;14(5):426–30.

6. Krizek TJ, Robson MC. Evolution of quantitative bacteriology in wound management. Am J Surg. 1975 Nov;130(5):579–84.

7. Schenker ML, Yannascoli S, Baldwin KD, Ahn J, Mehta S. Does timing to operative debridement affect infectious complications in open long-bone fractures? A systematic review. J Bone Joint Surg Am. 2012 Jun 20;94(12):1057–64.

8. Weber D, Dulai SK, Bergman J, Buckley R, Beaupre LA. Time to initial operative treatment following open fracture does not impact development of deep infection: a prospective cohort study of 736 subjects. J Orthop Trauma. 2014 Nov;28(11):613–9.

9. Hull PD, Johnson SC, Stephen DJG, Kreder HJ, Jenkinson RJ. Delayed debridement of severe open fractures is associated with a higher rate of deep infection. Bone Jt J. 2014 Mar;96–B(3):379–84.

10. C.L O, M M, N.M J. Controversies in the Management of Open Fractures. Open Orthop J. 2014 Jun 27;8:178–84.

11. Swiontkowski MF, Engelberg R, Martin DP, Agel J. Short musculoskeletal function assessment questionnaire: validity, reliability, and responsiveness. J Bone Joint Surg Am. 1999 Sep;81(9):1245–60.

12. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992 Jun;30(6):473–83.

13. Qi X, Yang DL, Qi F, Zhang QH, Wang JP. Statistical analysis on 2213 inpatients with traffic injuries from January 2003 to September 2005 in Ningbo city. Chin J Traumatol Zhonghua Chuang Shang Za Zhi. 2006 Aug;9(4):228–33.

14. Ibeanusi SEB, Ekere AU. Epidemiology of open tibial fractures in a teaching hospital. P H Med J. 2007 Jan 1;1(3):156–60.

15. Clelland SJ, Chauhan P, Mandari FN. The epidemiology and management of tibia and fibula fractures at Kilimanjaro Christian Medical Centre (KCMC) in Northern Tanzania. Pan Afr Med J [Internet]. 2016 Sep 29 [cited 2017 Sep 6];25. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5321146/

16. Gopinathan NR, Santhanam SS, Saibaba B, Dhillon MS. Epidemiology of lower limb musculoskeletal trauma with associated vascular injuries in a tertiary care institute in India. Indian J Orthop. 2017 Apr;51(2):199–204.

17. WHO | The burden of road traffic crashes, injuries and deaths in Africa: a systematic review and meta-analysis [Internet]. WHO. [cited 2017 Sep 6]. Available from: http://www.who.int/bulletin/volumes/94/7/15-163121/en/

18. Ruikar M. National statistics of road traffic accidents in India. J Orthop Traumatol Rehabil. 2013 Jan 1;6(1):1.

19. Rastogi D, Meena S, Sharma V, Singh GK. Causality of injury and outcome in patients admitted in a major trauma center in North India. Int J Crit Illn Inj Sci. 2014 Dec;4(4):298–302.

20. van Middendorp JJ, Sanchez GM, Burridge AL. The Edwin Smith papyrus: a clinical reappraisal of the oldest known document on spinal injuries. Eur Spine J. 2010 Nov;19(11):1815–23.

21. Blomstedt P. Orthopedic surgery in ancient Egypt. Acta Orthop. 2014 Dec;85(6):670–6.

22. Colton C. Orthopaedic challenges in Ancient Egypt. Bone Jt 360. 2013 Apr 1;2(2):2–7.

23. Guthrie HC, Clasper JC. Historical origins and current concepts of wound debridement. J R Army Med Corps. 2011 Jun;157(2):130–2.

24. Broughton G, Janis JE, Attinger CE. A brief history of wound care. Plast Reconstr Surg. 2006 Jun;117(7 Suppl):6S–11S.

25. Hindle P. Winner of the Frank Horan essay prize: the effect of war on the evolution of the treatment of open fractures. J Bone Joint Surg Br. 2010 Dec;92(12):1632–5.

26. Gabriel RA. Between Flesh and Steel: A History of Military Medicine from the Middle Ages to the War in Afghanistan. Potomac Books, Inc.; 2013. 313 p.

27. Browner BD, Levine AM, Jupiter JB, Trafton PG, Krettek C. Skeletal Trauma E-Book: 2-Volume Set. Elsevier Health Sciences; 2008. 3048 p.

28. Pape H-C, Webb LX. History of open wound and fracture treatment. J Orthop Trauma. 2008 Dec;22(10 Suppl):S133-134.

29. Granick MS, Gamelli RL. Surgical Wound Healing and Management. CRC Press; 2007. 186 p.

30. Pruitt BA. Combat Casualty Care and Surgical Progress. Ann Surg. 2006 Jun;243(6):715–29.

31. Helling TS, Daon E. In Flanders fields: the Great War, Antoine Depage, and the resurgence of débridement. Ann Surg. 1998 Aug;228(2):173–81.

32. Manring MM, Hawk A, Calhoun JH, Andersen RC. Treatment of War Wounds: A Historical Review. Clin Orthop. 2009 Aug;467(8):2168–91.

33. Chandler H, MacLeod K, Penn-Barwell JG. Extremity injuries sustained by the UK military in the Iraq and Afghanistan conflicts: 2003–2014. Injury. 2017 Jul 1;48(7):1439–43.

34. Covey DC. Conversion From Limb Salvage to Late Amputation: Lessons Learned From Recent Battlefields With Application to Civilian Trauma. J Surg Orthop Adv. 2015;24(3):170–3.

35. Stansbury LG, Branstetter JG, Lalliss SJ. Amputation in Military Trauma Surgery. J Trauma Inj Infect Crit Care. 2007 Oct 1;63(4):940–4.

36. Richardson RG. Larrey - what manner of man? Proc R Soc Med. 1977 Jul;70(7):490–4.

37. Johansen K, Daines M, Howey T, Helfet D, Hansen ST. Objective criteria accurately predict amputation following lower extremity trauma. J Trauma. 1990 May;30(5):568-572; discussion 572-573.

38. Helfet DL, Howey T, Sanders R, Johansen K. Limb salvage versus amputation. Preliminary results of the Mangled Extremity Severity Score. Clin Orthop. 1990 Jul;(256):80–6.

39. Slauterbeck JR, Britton C, Moneim MS, Clevenger FW. Mangled extremity severity score: an accurate guide to treatment of the severely injured upper extremity. J Orthop Trauma. 1994 Aug;8(4):282–5.

40. Sharma S, Devgan A, Marya KM, Rathee N. Critical evaluation of mangled extremity severity scoring system in Indian patients. Injury. 2003 Jul;34(7):493–6.

41. Brown KV, Ramasamy A, Mcleod J, Stapley S, Clasper JC. Predicting the Need for Early Amputation in Ballistic Mangled Extremity Injuries. J Trauma Inj Infect Crit Care [Internet]. 2009 Apr 1 [cited 2017 Sep 3];66(4). Available from: https://insights.ovid.com/pubmed?pmid=19359976

42. Court-Brown CM, Rimmer S, Prakash U, McQueen MM. The epidemiology of open long bone fractures. Injury. 1998 Sep 1;29(7):529–34.

43. Court-Brown CM, Bugler KE, Clement ND, Duckworth AD, McQueen MM. The epidemiology of open fractures in adults. A 15-year review. Injury. 2012 Jun;43(6):891–7.

44. Court-Brown CM, McQueen MM, Tornetta P. Trauma. Lippincott Williams & Wilkins; 2006. 584 p.

45. Praemer A, Furner S, Rice DP, American Academy of Orthopaedic Surgeons. Musculoskeletal conditions in the United States. Park Ridge, Ill.: American Academy of Orthopaedic Surgeons; 1992.

46. Cross WW, Swiontkowski MF. Treatment principles in the management of open fractures. Indian J Orthop. 2008;42(4):377–86.

47. Court-Brown CM, Caesar B. Epidemiology of adult fractures: A review. Injury. 2006 Aug 1;37(8):691–7.

48. Rockwood CA, Green DP, Bucholz RW. Rockwood & Green’s fractures in adults [Internet]. Philadelphia, PA: Lippincott, Williams & Wilkins; 2010 [cited 2017 Sep 6]. Available from: http://public.eblib.com/choice/publicfullrecord.aspx?p=3418106

49. Gustilo RB, Anderson JT. Prevention of infection in the treatment of one thousand and twenty-five open fractures of long bones: retrospective and prospective analyses. J Bone Joint Surg Am. 1976 Jun;58(4):453–8.

50. Gustilo RB, Mendoza RM, Williams DN. Problems in the management of type III (severe) open fractures: a new classification of type III open fractures. J Trauma. 1984 Aug;24(8):742–6.

51. Horn BD, Rettig ME. Interobserver reliability in the Gustilo and Anderson classification of open fractures. J Orthop Trauma. 1993;7(4):357–60.

52. Brand RA, Pape H-C. Biographical Sketch: Harald Tscherne, MD (1933–Present). Clin Orthop. 2013 Sep;471(9):2753–4.

53. Valderrama-Molina CO, Estrada-Castrillón M, Hincapie JA, Lugo-Agudelo LH. Intra- and interobserver agreement on the Oestern and Tscherne classification of soft tissue injury in periarticular lower-limb closed fractures. Colomb Médica CM. 45(4):173–8.

54. Fleming A. ON THE BACTERIOLOGY OF SEPTIC WOUNDS. The Lancet. 1915 Sep 18;186(4803):638–43.

55. Edwards R, Harding KG. Bacteria and wound healing. Curr Opin Infect Dis. 2004 Apr;17(2):91–6.

56. Otchwemah R, Grams V, Tjardes T, Shafizadeh S, Bäthis H, Maegele M, et al. Bacterial contamination of open fractures – pathogens, antibiotic resistances and therapeutic regimes in four hospitals of the trauma network Cologne, Germany. Injury. 2015 Oct 1;46:S104–8.

57. Patzakis MJ, Harvey JP, Ivler D. The role of antibiotics in the management of open fractures. J Bone Joint Surg Am. 1974 Apr;56(3):532–41.

58. Glass GE, Barrett SP, Sanderson F, Pearse MF, Nanchahal J. The microbiological basis for a revised antibiotic regimen in high-energy tibial fractures: preventing deep infections by nosocomial organisms. J Plast Reconstr Aesthetic Surg JPRAS. 2011 Mar;64(3):375–80.

59. Laxminarayan R, Duse A, Wattal C, Zaidi AKM, Wertheim HFL, Sumpradit N, et al. Antibiotic resistance-the need for global solutions. Lancet Infect Dis. 2013 Dec;13(12):1057–98.

60. Robinson D, On E, Hadas N, Halperin N, Hofman S, Boldur I. Microbiologic flora contaminating open fractures: its significance in the choice of primary antibiotic agents and the likelihood of deep wound infection. J Orthop Trauma. 1989;3(4):283–6.

61. Alonge TO, Ogunlade SO, Salawu SA, Fashina AN. Microbial isolates in open fractures seen in the accident and emergency unit of a teaching hospital in a developing country. West Afr J Med. 2002 Dec;21(4):302–4.

62. Bergman BR. Antibiotic prophylaxis in open and closed fractures: a controlled clinical trial. Acta Orthop Scand. 1982 Feb;53(1):57–62.

63. Katoch R, Rajagopalan S. Warfare Injuries: History, Triage, Transport and Field Hospital Setup in the Armed Forces. Med J Armed Forces India. 2010 Oct;66(4):304–8.

64. Robertson-Steel I. Evolution of triage systems. Emerg Med J EMJ. 2006 Feb;23(2):154–5.

65. Karamanou M, Rosenberg T, Liakakos T, Androutsos G. Baron Dominique-Jean Larrey (1766-1842): founder of military surgery and trauma care. Chir Buchar Rom 1990. 2011 Feb;106(1):7–10.

66. Bucholz RW. Rockwood and Green's Fractures in Adults: Two Volumes Plus Integrated Content Website (Rockwood, Green, and Wilkins' Fractures). Lippincott Williams & Wilkins; 2012. 2059 p.

67. Robinson PM, O'Meara MJ. The Thomas splint: ITS ORIGINS AND USE IN TRAUMA. Bone Jt J. 2009 Apr 1;91–B(4):540–4.

68. Paul GW. The history of external fixation. Clin Podiatr Med Surg. 2003 Jan;20(1):1–8, v.

69. Acute treatment of segmental tibial fractures with the Ilizarov method - Injury [Internet]. [cited 2017 Sep 11]. Available from: http://www.injuryjournal.com/article/S0020-1383(08)00332-X/abstract

70. Uhthoff HK, Poitras P, Backman DS. Internal plate fixation of fractures: short history and recent developments. J Orthop Sci. 2006 Mar;11(2):118–26.

71. Cronier P, Pietu G, Dujardin C, Bigorre N, Ducellier F, Gerard R. The concept of locking plates. Orthop Traumatol Surg Res OTSR. 2010 May 4;

72. Bhandari M, Guyatt GH, Tornetta P, Swiontkowski MF, Hanson B, Sprague S, et al. Current practice in the intramedullary nailing of tibial shaft fractures: an international survey. J Trauma. 2002 Oct;53(4):725–32.

73. SPRINT Investigators, Bhandari M, Tornetta P, Rampersad S-A, Sprague S, Heels-Ansdell D, et al. (Sample) size matters! An examination of sample size from the SPRINT trial study to prospectively evaluate reamed intramedullary nails in patients with tibial fractures. J Orthop Trauma. 2013 Apr;27(4):183–8.

74. Montgomery SR, Johnson JS, McAllister DR, Petrigliano FA. Surgical management of PCL injuries: indications, techniques, and outcomes. Curr Rev Musculoskelet Med. 2013 Jun;6(2):115–23.

75. Godina M. Early microsurgical reconstruction of complex trauma of the extremities. Plast Reconstr Surg. 1986 Sep;78(3):285–92.

76. Gopal S, Majumder S, Batchelor AG, Knight SL, De Boer P, Smith RM. Fix and flap: the radical orthopaedic and plastic treatment of severe open fractures of the tibia. J Bone Joint Surg Br. 2000 Sep;82(7):959–66.

77. D'Alleyrand J-CG, Manson TT, Dancy L, Castillo RC, Bertumen JBH, Meskey T, et al. Is time to flap coverage of open tibial fractures an independent predictor of flap-related complications? J Orthop Trauma. 2014 May;28(5):288–93.

78. Trueta J. Treatment of War Wounds and Fractures. Br Med J. 1942 May 16;1(4245):616–7.

79. Kindsfater K, Jonassen EA. Osteomyelitis in grade II and III open tibia fractures with late debridement. J Orthop Trauma. 1995 Apr;9(2):121–7.

80. Kreder HJ, Armstrong P. A review of open tibia fractures in children. J Pediatr Orthop. 1995 Aug;15(4):482–8.

81. Khatod M, Botte MJ, Hoyt DB, Meyer RS, Smith JM, Akeson WH. Outcomes in open tibia fractures: relationship between delay in treatment and infection. J Trauma. 2003 Nov;55(5):949–54.

82. Al-Arabi YB, Nader M, Nader M, Hamidian-Jahromi AR, Woods DA. The effect of the timing of antibiotics and surgical treatment on infection rates in open long-bone fractures: a 9-year prospective study from a district general hospital. Injury. 2007 Aug;38(8):900–5.

83. Tripuraneni K, Ganga S, Quinn R, Gehlert R. The effect of time delay to surgical debridement of open tibia shaft fractures on infection rate. Orthopedics. 2008 Dec;31(12).

84. Trickett RW, Rahman S, Page P, Pallister I. From guidelines to standards of care for open tibial fractures. Ann R Coll Surg Engl. 2015 Sep;97(6):469–75.

85. Duyos OA, Beaton-Comulada D, Davila-Parrilla A, Perez-Lopez JC, Ortiz K, Foy-Parrilla C, et al. Management of Open Tibial Shaft Fractures: Does the Timing of Surgery Affect Outcomes? J Am Acad Orthop Surg. 2017 Mar;25(3):230–8.

86. Kelsey JL, Thompson WD, Evans AS. Methods in Observational Epidemiology. Oxford University Press; 1986. 366 p.

87. Somford MP, van den Bekerom MPJ, Kloen P. Operative treatment for femoral shaft nonunions, a systematic review of the literature. Strateg Trauma Limb Reconstr. 2013 Aug;8(2):77–88.

88. Morshed S. Current Options for Determining Fracture Union. Adv Med [Internet]. 2014 [cited 2017 Sep 7];2014. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4590948/

89. Panteli M, Pountos I, Jones E, Giannoudis PV. Biological and molecular profile of fracture non-union tissue: current insights. J Cell Mol Med. 2015 Apr 1;19(4):685–713.

90. Cunningham BP, Brazina S, Morshed S, Miclau T. Fracture healing: A review of clinical, imaging and laboratory diagnostic options. Injury. 2017 Jun 1;48:S69–75.

91. Lazarus GS, Cooper DM, Knighton DR, Percoraro RE, Rodeheaver G, Robson MC. Definitions and guidelines for assessment of wounds and evaluation of healing. Wound Repair Regen Off Publ Wound Heal Soc Eur Tissue Repair Soc. 1994 Jul;2(3):165–70.

92. Menke NB, Ward KR, Witten TM, Bonchev DG, Diegelmann RF. Impaired wound healing. Clin Dermatol. 2007 Feb;25(1):19–25.

93. Douraiswami B, Dilip PK, Harish BN, Jagdish M. C-reactive protein and interleukin-6 levels in the early detection of infection after open fractures. J Orthop Surg Hong Kong. 2012 Dec;20(3):381–5.

94. Barei DP, Agel J, Swiontkowski MF. Current utilization, interpretation, and recommendations: the musculoskeletal function assessments (MFA/SMFA). J Orthop Trauma. 2007 Dec;21(10):738–42.

95. Westgeest J, Weber D, Dulai SK, Bergman JW, Buckley R, Beaupre LA. Factors Associated With Development of Nonunion or Delayed Healing After an Open Long Bone Fracture: A Prospective Cohort Study of 736 Subjects. J Orthop Trauma. 2016 Mar;30(3):149–55.

96. Pollak AN, Jones AL, Castillo RC, Bosse MJ, MacKenzie EJ, LEAP Study Group. The relationship between time to surgical debridement and incidence of infection after open high-energy lower extremity trauma. J Bone Joint Surg Am. 2010 Jan;92(1):7–15.

ANNEXURES

INSTITUTIONAL REVIEW BOARD AND FUNDING APPROVAL

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA.

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Alfred Job Daniel, D Ortho, MS Ortho, DNB Ortho
Chairperson, Research Committee & Principal

Dr. Nihal Thomas,
MD., MNAMS., DNB (Endo), FRACP (Endo), FRCP (Edin), FRCP (Glasg)
Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

November 21, 2015

Dr. Christina Marie Joseph
PG Registrar
Department of Orthopaedics,
Christian Medical College,
Vellore 632 004.

Sub: **Fluid Research grant project NEW PROPOSAL:**
Time to surgical debridement in open fractures of the lower limb and its effect on union and infections
Dr. Christina Marie Joseph, Emp. No. 29478, PG Registrar, Orthopaedics. Dr. ThilakJepegnanam, Emp. No. 20078, Dr. Vinoo Mathew Cherian, Emp. No. 14545, Dr. Manasseh Nithyananth, Emp. No. 28206, Dr. Viju Daniel Varghese, Emp. No. 28338, Dr. P.R.J.V.C. Boopalan, Emp. No. 28326, Orthopaedics. Dr. Thambu David Sudarsanam, Emp. No. 30008, Professor.

Ref: IRB Min No: 9693 [OBSERVE] dated 20.10.2015

Dear Dr. Christina Marie Joseph
The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "Time to surgical debridement in open fractures of the lower limb and its effect on union and infections" on September 01st 2015.

I enclose the following documents:-

1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Nihal Thomas, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. NIHAL THOMAS
MD.,MNAMS.,DNB(Endo),FRACP(Endo),FRCP(Edin),FRCP(Glasg)
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Cc: Dr. Thilak Jepegnanam, Dept. of Orthopaedics, CMC

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002.
Tel : 0416 - 2284294, 2284202 Fax : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA.

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Alfred Job Daniel, D Ortho, MS Ortho, DNB Ortho
Chairperson, Research Committee & Principal

Dr. Nihal Thomas,
MD., MNAMS., DNB (Endo), FRACP (Endo), FRCP (Edin), FRCP (Glasg)
Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

November 21, 2015

Dr. Christina Marie Joseph
PG Registrar
Department of Orthopaedics,
Christian Medical College,
Vellore 632 004.

Sub: **Fluid Research grant project NEW PROPOSAL:**
Time to surgical debridement in open fractures of the lower limb and its effect on union and infections

Dr. Christina Marie Joseph, Emp. No. 29478, PG Registrar, Orthopaedics. Dr. ThilakJepegnanam, Emp. No. 20078, Dr. Vinoo Mathew Cherian, Emp. No. 14545, Dr. Manasseh Nithyananth, Emp. No. 28206, Dr. Viju Daniel Varghese, Emp. No. 28338, Dr. P.R.J.V.C. Boopalan, Emp. No. 28326, Orthopaedics. Dr. Thambu David Sudarsanam, Emp. No. 30008, Professor.

Ref: IRB Min No: 9693 [OBSERVE] dated 20.10.2015

Dear Dr. Christina Marie Joseph
The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "Time to surgical debridement in open fractures of the lower limb and its effect on union and infections" on October 20th 2015.

The Committee raised the following documents

1. IRB Application format
2. Proforma
3. Questionnaire
4. Information Sheet and Informed Consent Form(English, Tamil, Telugu, Hindi)
5. No. of documents 1 - 4

The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on October 20th 2015 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA.

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Alfred Job Daniel, D Ortho, MS Ortho, DNB Ortho
Chairperson, Research Committee & Principal

Dr. Nihal Thomas,
MD., MNAMS., DNB (Endo), FRACP (Endo), FRCP (Edin), FRCP (Glasg)
Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

Name	Qualification	Designation	Affiliation
Dr. B. J. Prashantham	MA(Counseling Psychology), MA(Theology), Dr. Min(Clinical Counselling)	Chairperson, Ethics Committee, IRB. Director, Christian Counseling Centre, Vellore	External, Social Scientist
Dr. Nihal Thomas	MD, MNAMS, DNB(Endo), FRACP (Endo) FRCP(Edin) FRCP (Glasg)	Professor & Head, Endocrinology. Additional Vice Principal (Research), Deputy Chairperson (Research Committee), Member Secretary (Ethics Committee), IRB, CMC, Vellore	Internal, Clinician
Mrs. Pattabiraman	BSc, DSSA	Social Worker, Vellore	External, Lay Person
Dr. Rajesh Kannangai	MD, PhD.	Professor, Clinical Virology, CMC, Vellore	Internal, Clinician
Dr. Jayaprakash Muliyil	BSc, MBBS, MD, MPH, Dr PH (Epid), DMHC	Retired Professor, CMC, Vellore	External, Scientist &Epidemiologist
Mrs. Emily Daniel	MSc Nursing	Professor, Medical Surgical Nursing, CMC, Vellore	Internal, Nurse
Mrs. Sheela Durai	MSc Nursing	Professor, Medical Surgical Nursing, CMC, Vellore	Internal, Nurse
Mr. C. Sampath	BSc, BL	Advocate, Vellore	External, Legal Expert
Dr. Anuradha Rose	MBBS, MD, MHSC (Bioethics)	Associate Professor, Community Health, CMC, Vellore	Internal, Clinician
Dr. Vivek Mathew	MD (Gen. Med.) DM (Neuro)Dip. NB (Neuro)	Professor, Neurology, CMC, Vellore	Internal, Clinician
Dr. Chandrasingh	MS, MCH, DMB	Professor, Urology,CMC, Vellore	Internal, Clinician

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002.
Tel : 0416 - 2284294, 2284202 Fax : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Alfred Job Daniel, D Ortho, MS Ortho, DNB Ortho
Chairperson, Research Committee & Principal

Dr. Nihal Thomas,
MD., MNAMS., DNB (Endo), FRACP (Endo), FRCP (Edin), FRCP (Glasg)
Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

Ms. Grace Rebecca	M.sc (Biostatistics)	Lecturer, Biostatistics, CMC, Vellore	Internal, Statistician
Dr. Simon Pavamani	MBBS, MD	Professor, Radiotherapy, CMC, Vellore	Internal, Clinician
Dr. Inian Samarasam	MS, FRCS, FRACS	Professor, Surgery, CMC, Vellore	Internal, Clinician
Dr. Balamugesh	MBBS, MD(Int Med), DM, FCCP (USA)	Professor, Pulmonary Medicine, CMC, Vellore	Internal, Clinician
Dr. Niranjan Thomas	DCH, MD, DNB (Paediatrics)	Professor, Neonatology, CMC, Vellore	Internal, Clinician
Dr. Mathew Joseph	MBBS, MCH	Professor, Neurosurgery, CMC, Vellore	Internal, Clinician
Dr. RatnaPrabha	MBBS, MD	Associate Professor, Clinical Pharmacology, CMC, Vellore.	Internal, Pharmacologist

We approve the project to be conducted as presented.

Kindly provide the total number of patients enrolled in your study and the total number of withdrawals for the study entitled: "Time to surgical debridement in open fractures of the lower limb and its effect on union and infections" on a monthly basis. Please send copies of this to the Research Office (research@cmcvellore.ac.in)

Fluid Grant Allocation:

A sum of 68,500/- INR (Sixty Eight Thousand five hundredOnly) will be granted for 15Months and out of which a maximum of Rs.5000/- can be spent for stationery, printing, Xeroxing and computer charges(if computers used are within the institution)

Yours sincerely

Dr. NIHAL THOMAS
MD.,MNAMS.,DNB(Endo),FRACP(Endo),FRCP(Edin),FRCP(Glasg)
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

IRB Min No: 9693 [OBSERVE] dated 20.10.2015

DATA ENTRY PROFORMA

PATIENT CONSENT OBTAINED: YES/NO

PATIENT'S NAME AGE: ______ GENDER:

HOSPITAL NO:

CONTACT DETAILS:-

PHONE NO:

ADDRESS ....

....

COMORBID CONDITIONS:

	YES	NO
SMOKING		
ALCOHOL CONSUMPTION		
DIABETES MELLITUS		
HYPERTENSION		
COPD/ASTHMA		
ANEMIA- Hb (<10g/dl)		
MALNUTRITION OBESITY		

BMI:.........................

OBESITY:...

ORTHOPAEDIC UNIT: 1 / 3

DUTY TEAM: ____.

DATE OF INJURY: ________________ TIME OF INJURY:______________ AM/PM.

MECHANISM OF INJURY:

FALL	INJURY	ASSAULT	MVA*	CRUSH	OTHERS

*MVA: - Motor Vehicle accident

DATE OF EXAMINATION:________________. TIME OF EXAMINATION ______________ AM/PM .

SITE OF FRACTURE:

	AO CLASSIFICATION
FEMUR	
TIBIA	

FIBULA	

CONTAMINATION: YE**S**/NO

DISTAL PULSES: YES/NO

IF NO; DOPPLER/ANGIOGRAM: NORMAL / ABNORMAL

NEUROLOGICAL DEFICTIS: YES/NO

ASSOCIATED INJURIES:-

1)

2)

3)

4)

5)

GUSTILO AND ANDERSON CLASSIFICATION:

1	2	3A	3B	3C

ABBREVIATED INJURY SCALE:-

1	2	3	4	5	6

ISS SCORE:-

AMERICAN SOCIETY OF ANESTHESIOLOGISTS CLASSIFICATION:-

1	2	3	4	5	6

ASA -EMERGENCY SURGERY (E): YES/NO

TREATMENT PLAN (as decided by the operating surgeon in charge)

AT THE TIME OF ASSESSMENT:____.

____.

BLOOD TRANSFUSION: YES/NO

TIME OF INJURY TO ANTIBIOTIC ADMINISTRATION: ______________________.

TIME DELAY TO SURGICAL DEBRIDEMENT: ______________________________.

NAME OF OPERATING SURGEON: _______________________________________.

CONSULTANT/REGISTRAR:-

NUMBER OF YEARS OF SURGICAL EXPERIENCE:____________________.

METHOD OF SKELETAL STABILIZATION: ____.

	YES	NO
EXTERNAL FIXATOR		
ORTHOFIX		
ILIZAROV'S		
NAIL		
PLATE		
SCREW		
K-WIRE/RUSH ROD		

WOUND CLOSURE:

PRIMARY	DELAYED/SECONDARY	STSG	FREE FLAP	LOCAL FLAP

CHANGE IN THE INITIAL TREATMENT PLAN: YES/NO

IF YES, SPECIFY: ____.

DATE OF ADMISSION: DATE OF DISCHARGE:

TOTAL DURATION OF HOSPITAL STAY:

ICU STAY: YES /NO

IF YES, DURATION OF STAY

ANY OTHER ASSOCIATED COMPLICATIONS: IMPLANT FAILURE..................

IP BILL: ....

OUTCOME:-

A) WOUND INFECTION:

1) AT 1 Month – YES/NO

CRP:

3) CULTURE PROVEN INFECTION: YES/NO

4) ANY WOUND DISCHARGE POST SURGERY REQUIRING ANTIBIOTIC COURSE/READMISSION

YES/NO

IF RE- ADMISSION

DOA	DOD	DURATION OF HOSPITAL STAY	ADDITIONAL EXPENDITURE (IP BILL)

ANY ASSOCIATED COMPLICATIONS……………………………………………………………………………………

5) SECONDARY PROCEDURE (DEBRIDEMENT/ DEFINITIVE SURGERY) : YES/NO

IF YES

DOA	DOD	NAME OF PROCEDURE	DURATION OF HOSPITAL STAY	ADDITIONAL EXPENDITURE (IP BILL)

ANY ASSOCIATED COMPLICATIONS……………………………………………………………………………………

B) FRACTURE UNION

COMMENTS:-

AT 9 MONTHS POST INJURY:

FRACTURE UNITED: YES/NO

TIME TO FRACTURE UNION: ……………………..MONTHS

C) FUNCTIONAL OUTCOME AT 9 MONTHS POST INJURY; :- RETURN TO WORK: - YES/NO

SMFA SCORE:…………………………

SF 36 SCORE:…………………………

Non-union and infections in open fractures of the lower limb

Information sheet

We are doing an observational study on open fractures. I am going to give you information and invite you to be a part of this study.
The incidence of road traffic accidents are increasing worldwide. Fractures are one of the commonest injuries following road traffic accidents. Among open fractures, lower extremity is more commonly involved compared to the upper extremity.

You are requested to participate in our study where we will record the total time period from your injury till the start of surgery

We will study the outcome post surgery, whether you have any infection and the time your fracture takes to unite. We will also follow up your hospital progress records and the functional status of your limb over time. A blood test will also be required of you after 1 month to determine presence of any infection.

You are being chosen because you are one among the patients with open long bone fractures of the lower limb.
Your name, identity and other personal information that we collect from this research project will be kept confidential and will not be shared with or given to anyone except those involved in the research.
We may share the knowledge that we get from doing this research through publications strictly excluding any confidential information.
You do not have to take part in this study if you do not wish to do, participation is purely voluntary and refusing to participate will not affect your treatment at this hospital in any way. You will still have all the benefits that you would otherwise have at this hospital. If you have any questions you may ask them now or later, even after the study has started. If you wish to ask questions later, you may contact any of the following:-

Name:-Dr Christina Marie Joseph

Address: - CMC Vellore, Department of Orthopaedics, 2282020, 2282091

INFORMED CONSENT FORM

Study Title: Non-union and infections in open fractures of the lower limb

Name of the principal investigator: Dr Christina Marie Joseph **Study No:-**

Subject's Name: __________________Age: ______________________

(i) I confirm that I have read and understood the information sheet. I have had the opportunity to ask questions.

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

(iii) I understand that the study staff, institutional ethics committee members and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the study. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published.

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s).

(v) I agree to take part in the above study.

Date: _____/_____/______ Signature (or Thumb impression) of the Subject

Study investigator's name: Signature:

____

Witness name: Signature or thumb impression:

____

DATA- EXCEL SHEET 2016

ID	HRS TO DELAY	INF-	NON-UNION	CRP	G	# Site 1-Femur 2. Leg	FIX-	AGE	SEX	SMOKING	ASA	ISS	ADD SX
1	13.4	0	0	3.17	3B	1	3	25	M	0	1	17	1
2	14.54	0	1	37.4	3B	2	3	30	F	0	1	14	3
3	11.5	1	0	3.17	3B	1	3	37	F	0	1	17	1
3	11.5	0	0	3.17	3B	2	3	37	F	0	1	17	0
4	95	0	0	11.1	3B	2	2	19	M	0	5	27	0
5	10.5	0	0	12	3B	1	3	22	M	0	1	11	0
6	40.45	1	0	31	3A	1	3	17	M	0	5	22	2
7	15.5	0	0	3.43	3A	2	2	62	F	0	2	14	0
7	15.5	0	0	3.43	3A	1	3	62	F	0	2	14	0
8	40.19	0	0	29	3B	1	3	52	F	0	1	22	2
9	21	0	0	29.4	3A	2	3	20	M	0	1	19	0
10	20	0	0	7.78	3A	2	3	47	M	1	2	14	0
11	120	1	0	19.2	3B	1	3	39	M	1	1	14	1
12	11.4	1	0	3.77	3B	2	3	25	M	0	1	11	1
13	14.1	0	1	3.27	3B	2	3	37	M	1	2	14	0
14	26.1	0	1	3.27	3A	2	3	30	M	1	2	14	1
15	26.1	0	0	3.27	3A	2	3	41	F	0	2	22	0
16	10.33	0	0	6.07	3B	2	3	45	M	1	2	14	0
17	28.4	0	1	8.93	3B	2	2	60	M	1	3	14	0
18	12.33	0	0	59.8	3B	2	1	27	M	0	1	27	1
19	18.33	1	1	19.6	3A	2	3	57	M	1	2	14	2
20	15.5	0	0	7.92	3A	1	1	37	M	1	2	17	0
21	5.24	0	0	3.27	3B	2	3	62	M	1	3	14	0
21	5.24	0	0	3.27	3B	1	3	62	M	1	3	14	0
22	11.33	0	0	5.52	3B	2	3	36	M	1	1	14	0
22	11.33	1	0	5.52	3B	1	3	36	M	1	1	14	1
23	23.5	0	1	5.01	3B	1	2	26	M	0	2	11	1
24	24.41	1	AMP	201	3B	2	2	52	F	0	1	19	3
25	10.21	0	0	3.17	3A	2	3	26	F	0	1	14	0
26	27.5	0	0	3.17	3A	2	3	37	M	1	2	24	0
27	20.29	1	1	10.8	3B	2	2	48	M	1	1	9	2
28	12.6	0	0	12.5	3A	2	3	23	M	0	1	9	0
29	14.6	0	0	3.14	3A	1	3	22	M	0	1	6	1
30	26.1	1	0	18.1	3B	2	2	31	M	0	1	9	1
31	13.5	1	AMP	83.2	3B	2	3	74	M	1	2	9	2
31	13.5	1	AMP	83.2	3B	1	3	74	M	1	2	9	0
32	11.32	0	0	4.05	3B	1	3	44	M	1	1	22	0
32	11.32	0	0	4.05	3B	2	3	44	M	1	1	22	0
33	18.45	0	0	3.27	3A	2	3	30	M	0	1	6	0
34	24.1	0	0	8.05	3A	1	3	41	M	0	1	11	0

35	15.33	0	0	4.28	3A	2	3	33	F	0	1	6	1
36	9.5	0	0	3.93	3C	2	2	54	F	0	1	9	1
37	32.6	1	0	91.4	3B	2	2	56	M	0	2	24	0
38	22.5	1	0	22.3	3B	1	3	66	M	1	2	14	0
39	15.8	0	DEATH	148	3B	1	3	57	M	0	1	11	1
40	15.6	0	0	13.5	3A	1	3	19	M	0	1	6	0
41	40	0	1	5.92	3A	2	1	60	F	0	3	18	0
42	26.1	0	0	9.03	3A	2	3	73	M	0	1	9	0
43	8.32	0	1	3.16	3B	2	3	26	M	1	1	9	0
44	30.33	1	1	34.3	3B	2	3	62	M	1	2	9	1
45	19.45	0	1	3.17	3B	2	3	66	M	0	1	9	0
46	9.3	0	1	3.46	3B	1	3	46	M	1	1	11	2
47	7.5	0	0	3.17	3B	2	3	24	M	1	1	9	3
47	7.5	0	0	3.17	3B	1	3	24	M	1	1	9	0
48	14.33	1	1	54.2	3B	2	2	45	M	1	2	9	1
49	5.32	0	0	3.17	3B	2	3	59	M	0	1	9	0
50	19.9	1	1	3.84	3B	2	3	38	M	1	1	9	2
51	19.2	0	1	3.24	3B	2	3	45	M	1	1	9	0
52	22.4	0	0	14.1	3B	1	3	30	M	1	1	6	0
53	52.1	1	0	109	3B	2	3	37	M	1	1	9	0
54	30.3	0	1	9.31	3A	2	3	33	M	1	1	11	0
55	28.1	0	1	3.14	3A	1	3	29	M	1	1	14	0
56	46.5	1	DEATH	DEATH	3B	1	3	52	M	1	2	14	0
57	24.4	1	0	3.17	3B	2	2	65	M	1	2	9	1
57	24.4	1	0	3.17	3B	1	2	65	M	1	2	9	0
58	48.11	0	0	5.64	3A	2	3	31	M	0	1	6	1
59	14.5	0	0	3.17	3A	1	3	17	M	0	1	6	0
60	19.5	1	AMP	118.25	3B	2	2	42	M	0	3	28	1
61	30.5	1	1	22.7	3C	2	3	28	M	0	1	9	5
62	15.5	0	0	3.19	3A	2	3	61	M	1	1	9	0
63	14.33	1	0	109	3B	2	3	65	M	1	3	13	5
64	18.33	0	0	5.07	3A	2	3	48	M	1	1	14	0
65	18.1	0	1	6.99	3B	2	3	32	M	1	1	11	0
66	18.5	0	0	6.37	3A	1	3	54	M	1	2	6	1
67	14.33	1	0	179	3A	1	3	32	M	1	2	11	1
68	15.4	0	0	3.17	3A	1	1	36	F	0	1	6	0
69	15.8	0	0	37.8	3B	2	3	26	M	1	1	14	2
70	42.3	1	1	5.51	3B	1	3	44	F	0	2	12	1
70	42.3	0	1	5.51	3B	2	3	44	F	0	2	12	0
71	16.5	0	0	3.81	3A	2	3	25	M	0	1	6	0
72	30.1	1	0	11.6	3B	2	2	67	M	0	1	9	1
73	22.3	1	1	139	3B	1	3	47	M	1	2	17	3
74	10.5	0	0	3.17	3B	2	3	73	M	1	1	9	0
75	14.15	0	0	107	3A	1	3	27	M	0	1	17	0

76	11.3	0	0	3.16	3B	2	3	47	M	0	1	9	1
76	11.3	0	0	3.16	3B	1	3	47	M	0	1	9	0
77	7.5	0	0	6.44	3B	2	3	17	M	0	1	6	0
77	7.5	0	0	6.44	3B	1	3	17	M	0	1	6	0
78	13.5	0	1	3.14	3A	2	3	47	M	0	1	6	1
79	8.5	3	0	3.17	3B	2	2	28	M	0	1	9	2
80	16.5	0	1	8.05	3A	2	3	40	F	0	3	14	1
81	11.5	0	0	3.17	3B	1	3	67	M	0	1	14	0
82	9.5	0	0	3.17	3B	2	3	31	M	0	1	14	1
83	114.5	1	1	15	3A	1	3	77	F	0	2	11	1
84	25.2	0	0	3.17	3A	2	3	24	M	0	1	6	0
85	20.5	1	1	5	3A	2	2	27	M	1	1	6	2
86	4.5	0	1	8.9	3B	1	2	36	M	0	1	22	0
86	4.5	0	0	8.9	3B	2	2	36	M	0	1	22	3
87	7.3	0	1	3.17	3B	2	3	48	M	1	1	9	1
88	19	0	DEATH	DEATH	3B	2	1	75	M	0	2	17	0
89	16.5	0	0	14.4	3B	1	3	18	M	0	1	11	0
90	120	1	1	11.9	3A	2	2	19	M	0	1	29	2
91	164	1	1	142	3B	1	3	39	M	0	1	6	3
92	50	1	1	8.13	3B	2	3	66	F	0	1	6	2
92	50	1	1	8.13	3B	1	3	66	F	0	1	6	0
93	5.5	0	0	7.95	3B	2	3	57	F	0	1	9	0
94	8.5	1	1	4.28	3B	2	3	22	M	0	1	9	2
95	15.5	0	0	3.17	3A	2	3	52	M	0	1	9	0
95	15.5	0	0	3.17	3A	1	3	52	M	0	1	9	2
96	15.6	0	0	3.16	3A	1	3	27	M	1	1	6	0
97	22.2	1	1	3.16	3B	2	2	57	F	0	1	6	2
98	18.5	1	1	33.3	3B	2	3	62	M	1	2	9	0
98	18.5	1	1	33.3	3B	1	3	62	M	1	2	9	4
99	17.5	1	0	9.61	3B	2	3	38	F	0	1	9	3
100	14.6	1	1	8.65	3C	2	2	29	M	1	2	14	4
101	15.6	0	0	3.16	3A	1	3	24	M	1	1	14	1
102	8.5	0	0	3.7	3B	2	2	31	F	0	1	9	1
103	11.5	1	0	5.55	3B	2	2	58	F	0	1	29	2
104	5.5	0	0	3.16	3B	2	1	25	M	0	1	6	0
105	22.5	0	0	3.16	3B	2	3	19	M	0	1	9	0
106	14.5	0	0	9.88	3B	1	3	55	M	0	1	9	0
107	10.5	0	0	3.17	3A	2	2	47	M	0	1	9	1
108	28.5	1	1	3.14	3B	2	2	40	M	1	2	17	1
109	13.5	1	0	6.13	3A	1	3	30	M	1	1	6	1
110	34.2	0	1	101	3B	1	3	23	M	0	1	17	1
111	40	1	1	3.17	3B	2	3	30	M	1	1	9	2
112	17.5	0	1	3.14	3B	2	3	53	M	0	1	9	0
113	14.5	0	0	3.17	3A	2	3	49	M	0	1	9	1

113	14.5	0	0	3.17	3A	1	3	49	M	0	1	9	0
114	6.5	0	0	3.16	3B	2	3	61	M	1	1	9	0
114	6.5	0	0	3.16	3B	1	3	61	M	1	1	9	0
115	17.33	1	0	3.14	3B	2	2	57	M	1	2	9	1
115	17.33	1	0	3.14	3B	1	3	57	M	1	2	9	0
116	9.5	0	0	3.17	3A	1	3	21	M	1	4	34	2
116	9.5	0	0	3.17	3B	2	2	21	M	1	4	34	0
117	11.9	0	0	3.14	3A	2	3	20	M	1	1	9	0
118	15.5	1	1	11.5	3B	2	3	55	M	0	1	9	2
119	11.4	0	0	3.17	3C	2	1	37	M	0	1	9	0
120	14.6	1	0	3.17	3B	2	3	19	M	0	1	9	1
121	17.5	3	1	3.14	3B	2	2	49	M	1	1	9	1
122	50	1	0	33.8	3B	1	3	27	M	0	5	29	1
123	16.5	1	1	12	3B	1	3	49	M	0	2	17	0
124	24.2	1	1	3.17	3B	1	3	30	M	0	1	9	0
125	34.4	1	1	146	3B	1	3	64	F	0	1	17	3
125	34.4	1	0	146	3B	2	3	64	F	0	1	17	0
126	14.4	0	0	175	3A	1	3	40	M	0	1	11	0
127	44.3	0	0	6.48	3A	2	2	59	M	0	1	9	0
128	20.3	0	0	8.35	3A	1	1	31	M	1	1	6	0
129	30.5	1	0	12.2	3B	2	2	66	M	1	2	9	1
129	30.5	1	0	12.2	3B	1	3	66	M	1	2	9	0
130	8.7	0	0	3.16	3C	2	2	30	M	1	1	14	0
131	14.6	1	AMP	18.9	3B	1	3	21	M	0	1	14	0
131	14.6	1	AMP	18.9	3B	2	2	21	M	0	1	14	6
132	14.57	1	AMP	25.9	3C	2	2	42	M	1	2	14	3
133	20.5	1	1	3.17	3A	1	3	20	M	1	1	11	1
134	16.5	0	0	3.17	3B	1	3	20	M	1	1	14	1
135	120	1	1	3.14	3B	1	3	25	M	1	2	11	4
136	13.3	0	0	9.87	3A	2	3	23	M	1	2	9	0
137	15.6	1	1	9.94	3B	2	2	17	M	0	1	14	3
138	30.5	1	0	127	3B	1	2	37	M	1	1	9	2
139	93	0	1	15	3B	2	2	43	M	0	1	9	0
140	22.5	0	1	8.17	3A	2	3	58	M	1	1	6	0
141	14.28	1	1	3.49	3B	1	3	28	M	1	2	14	0
141	14.28	1	1	3.49	3B	2	3	28	M	1	2	14	1
142	16.59	0	0	13.5	3A	1	3	19	M	0	1	11	0
143	5.55	0	0	3.17	3C	1	3	28	M	1	1	22	0
143	5.55	0	0	3.17	3B	2	3	28	M	1	1	22	0
144	23.1	1	1	82.8	3B	2	2	70	M	1	3	17	0
145	5.4	0	0	3.17	3A	2	1	72	M	1	1	11	0
146	17.5	0	0	3.17	3A	1	3	20	M	1	1	14	0
147	7.5	3	0	151	3B	2	2	28	M	1	1	9	1
148	35.59	0	1	90	3B	2	3	46	M	1	2	9	1

149	12.3	0	0	3.14	3B	2	3	61	F	0	1	9	0
149	12.3	0	0	3.14	3B	1	3	61	F	0	1	9	0
150	11.5	0	0	3.14	3B	2	3	65	M	0	1	6	0
151	13.5	0	1	7.38	3B	1	3	51	M	0	1	11	0
152	75.33	1	0	191	3B	2	3	25	M	0	1	9	0
152	75.33	1	1	191	3B	1	3	25	M	0	1	9	0
153	14.5	0	0	4.45	3B	1	3	35	M	0	1	14	2
153	14.5	0	0	4.45	3B	2	3	35	M	0	1	14	0
154	19.54	0	1	23	3B	2	2	31	M	0	1	9	1
155	32.66	1	1	14.3	3A	2	2	33	M	0	1	6	0
156	15.2	1	0	69.8	3B	2	3	31	M	0	1	9	1
157	16.54	0	1	10	3A	2	3	64	M	1	1	17	1
158	11.5	0	0	3.17	3A	2	3	42	F	0	1	9	0
159	6.5	0	0	3.14	3A	2	2	29	F	0	1	22	0
160	15.6	1	1	3.14	3A	1	3	47	M	0	1	11	1
161	18.36	1	0	6.61	3B	1	3	27	M	1	1	11	1
162	20.54	1	1	32.7	3B	1	2	38	M	0	2	22	2
163	9.5	0	0	6.08	3B	1	2	44	M	0	1	17	0
163	9.5	0	0	6.08	3B	2	2	44	M	0	1	17	0
164	46.5	0	0	3.14	3B	2	3	33	M	0	1	17	0
165	14.35	0	0	3.14	3B	2	3	48	M	0	1	9	0
165	14.35	0	0	3.14	3B	1	3	48	M	0	1	9	0
166	9.33	0	0	3.14	3B	2	3	52	M	0	1	6	1
167	12.2	0	0	3.17	3B	2	3	25	M	0	1	9	0
168	28.5	3	1	13.7	3B	2	2	19	M	1	1	6	0
169	14.45	0	0	3.14	3A	2	3	35	M	0	2	22	1